

**SLEEP-DISORDERED BREATHING  
AND  
CHRONIC HEART FAILURE**

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## ABSTRACT

**Background** Chronic heart failure, a common cause of morbidity and mortality, is frequently associated with sleep-disordered breathing, which may be detrimental through a variety of haemodynamic, autonomic and vascular mechanisms. Whilst associated with increased morbidity and mortality, sleep-disordered breathing is often unrecognised and yet presents a potential therapeutic target in patients with chronic heart failure.

**Objectives** The aims of the thesis were, in patients with stable symptomatic chronic heart failure treated with optimal contemporary heart failure therapy: first, to determine prospectively the prevalence of sleep-disordered breathing; second, to compare the clinical characteristics of those patients with sleep-disordered breathing to those without sleep-disordered breathing; third, to assess the accuracy and clinical utility of a limited sleep study system, compared with polysomnography, for diagnosing sleep-disordered breathing; and finally, fourth, to establish whether treatment of obstructive sleep apnoea with nocturnal continuous positive airway pressure improves subjective and objective measures of heart failure severity.

**Methods** Patients with stable symptomatic chronic heart failure were screened for sleep-disordered breathing by home sleep study. Daytime sleepiness was assessed by Epworth Sleepiness Scale and heart failure severity by symptom class, left ventricular ejection fraction and serum N-terminal pro-brain natriuretic peptide concentrations. In a subset of patients, synchronous in-laboratory limited sleep studies and polysomnography, and home limited sleep studies, were performed prospectively. Patients with obstructive sleep apnoea and stable symptomatic chronic heart failure were randomised to nocturnal auto-titrating continuous positive airway pressure or sham for six weeks each in crossover design. Study co-primary endpoints were changes in peak  $\text{VO}_2$  and six minute walk distance and secondary endpoints changes in left ventricular ejection fraction,  $\text{VE}/\text{VCO}_2$  slope, neurohormonal markers and quality of life.

**Results** In the era of modern therapy, sleep-disordered breathing is common in patients with stable symptomatic chronic heart failure, predominantly obstructive in aetiology, without clear relationship to heart failure severity and is difficult to diagnose because of major overlap in symptomatology. Limited sleep studies compare well diagnostically to polysomnography when tested under identical patient and environmental conditions but less so when tested in the home setting. Auto-titrating continuous positive airway pressure improves daytime sleepiness in patients with obstructive sleep apnoea and chronic heart failure but not other subjective or objective measures of heart failure severity.

**Conclusions** Sleep-disordered breathing is difficult to detect clinically in patients with chronic heart failure, and as such, the diagnosis is reliant on accurate sleep studies. However, the clinical utility of limited sleep studies in detection and diagnosis of sleep-disordered breathing is restricted by a number of technical and situational factors which are exacerbated in patients with chronic heart failure. The potential therapeutic benefits of continuous positive airway pressure in patients with obstructive sleep apnoea and chronic heart failure are achieved by alleviation of obstructive sleep apnoea rather than by improvement in cardiac function; however, efficacy of continuous positive airway pressure therapy may in part be limited by poor patient tolerability and compliance.

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## DECLARATION

This thesis represents research undertaken in the Department of Cardiology and the Wellcome Trust Clinical Research Facility at the Western General Hospital, the Departments of Cardiology and Sleep Medicine at the Royal Infirmary, Edinburgh, and the Scottish Cardiopulmonary Transplant Unit, Glasgow. The work described has been my own and carried out during the period between 2002 and 2005 whilst a Clinical Research Fellow in Cardiology at the University of Edinburgh. I have been fortunate in gaining the advice and assistance of many colleagues, and they have been formally acknowledged. The work has been published in peer reviewed journals: see appendix. The thesis has not been accepted in any previous applications for a degree and all sources of information have been acknowledged.

Lindsay Anne Smith

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I dedicate this thesis to my parents, for the opportunities they have offered me.

## ABBREVIATIONS

ACE	Angiotensin converting enzyme
AHI	Apnoea hypopnoea index
ARB	Angiotensin receptor blocker
ASV	Adaptive servo-ventilation
BMI	Body mass index
CANPAP	Canadian Positive Airway Pressure for Treatment of Central Sleep Apnea in Heart Failure
CHF	Chronic heart failure
CPAP	Continuous positive airway pressure
CSA	Central sleep apnoea
CSR	Cheyne Stokes respiration
EDTA	Ethylene diamine tetraacetic acid
EEG	Electro-encephalogram
EMG	Electromyogram
EOG	Electro-oculogram
ESS	Epworth sleepiness scale
LVEF	Left ventricular ejection fraction
LVESD	Left ventricular end-systolic dimension
LVEDD	Left ventricular end-diastolic dimension
NREM	Non-rapid eye movement
NT-proANP	N-terminal pro-atrial natriuretic peptide
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
OSA	Obstructive sleep apnoea
OSAHS	Obstructive sleep apnoea hypopnoea syndrome
OSLER	Oxford SLEep Resistance
PSG	Polysomnography
REM	Rapid eye movement
RERA	Respiratory effort related arousal
SDB	Sleep-disordered breathing

## **CHAPTER 1**

### **INTRODUCTION:**

# **SLEEP-DISORDERED BREATHING AND CHRONIC HEART FAILURE**



## **1.1 DEFINITIONS AND EPIDEMIOLOGY**

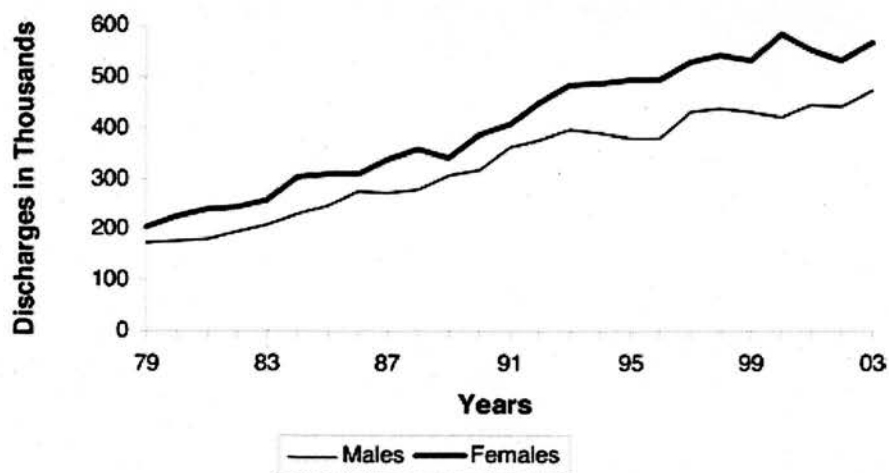
### **1.1.1 Chronic Heart Failure**

Chronic heart failure (CHF) is a complex clinical syndrome resulting from structural or functional cardiac disorder which impairs the ability of the left ventricle to fill with or eject blood. It is characterized by dyspnoea and fatigue, which may limit exercise tolerance, and fluid retention, which may cause peripheral oedema and pulmonary congestion.(1) Potential underlying causes of CHF are therefore numerous, but ischaemic heart disease is the most common in developed countries. Epidemiological studies have identified hypertension, diabetes mellitus, obesity and smoking as risk factors for the development of CHF.(2)

CHF is a major cause of morbidity and mortality in developed countries and its prevalence and incidence continue to rise.(3) In the United States it is estimated 5 million people are receiving treatment for CHF, there are 550 000 new cases each year and CHF contributes to almost 287 000 deaths per year.(4) These observations have led to suggestions that CHF is a 'disease of epidemic proportions', both in the United States and in Europe.(5;6) Potential explanations for the increasing morbidity and mortality associated with CHF (figure 1.1) include an ageing population and reducing acute cardiovascular mortality. The resulting clinical and economic burden on healthcare systems and society, through direct medical costs, disability and loss of employment, is great; indeed the estimated direct and indirect cost of CHF in the United States for 2006 was \$29.6 billion. (4)

**Figure 1.1**

Hospital discharges for heart failure by sex (United States: 1970–2003). Note: Hospital discharges include people discharged alive and dead. Source: National Hospital Discharge Survey, CDC/NCHS and NHLBI.



Current management guidelines, after identification and treatment of treatable causes, recommend dietary and lifestyle advice, optimisation of drug and device therapy and, in appropriate cases, consideration of advanced CHF therapies such as left ventricular assist devices and heart transplantation, all in the context of a program of regular monitoring by healthcare professionals.(1;7) There have been important recent advances in drug and device therapy for patients with CHF with ACE inhibition, angiotensin receptor blockade, beta-blockade, spironolactone, cardiac resynchronisation and implantable defibrillator therapy all having proven morbidity and mortality benefits.(8-17) Series of clinical trials have demonstrated improvements in survival of patients with CHF with changes in baseline therapy. Whereas patients with symptomatic CHF treated with digoxin and diuretic therapy in the Veterans Administration Cooperative study had a 2 year mortality rate of 34%, the recent COMPANION trial reported a 1 year mortality of <10% in similar patients treated with ACE inhibition, beta-blockade and aldosterone antagonism.(8;18) However, despite these advances, patients with CHF still follow a typical course of declining quality of life, frequent hospital admissions, and ultimately premature death from progressive pump failure or cardiac arrhythmias. The identification of potential exacerbating factors and possible therapeutic targets therefore remains extremely important.

### **1.1.2 Sleep-Disordered Breathing**

Non-rapid eye movement (NREM) sleep, accounting typically for 85% of total sleep, is a period of cardiovascular relaxation characterized by decreased heart rate, cardiac output, systemic vascular resistance, metabolic rate and sympathetic nervous system activity.(19-21) In contrast rapid eye movement (REM) sleep, approximately 15% of

total sleep, is associated with intermittent bursts of sympathetic nervous system activity; because NREM sleep is dominant, average sleeping blood pressure and heart rate remain lower than during waking hours.(20) Sleep is generally reduced and of poorer quality in patients with CHF.(22-24) The presence of sleep-disordered breathing (SDB) may further disrupt the normal relaxant effects of sleep on the cardiovascular system with detrimental consequences.

Sleep-disordered breathing is characterised by recurrent apnoeas and hypopnoeas causing disruption of normal ventilation and sleep architecture. Cessation of breathing may be due to upper airway obstruction (obstructive; see figure 1.2), loss of ventilatory effort (central; see figure 1.3) or a combination of both (mixed). Upper airway obstruction leads to increasing effort to produce airflow resulting in increasing thoraco-abdominal wall movements which are out of phase. In contrast, central sleep apnea is characterized by absence of thoraco-abdominal movement. Cheyne-Stokes respiration (CSR) is a particular form of central sleep apnea which was reported by John Cheyne and William Stokes in a patient with heart failure in 1818, and previously observed by another physician, John Hunter.(25-28) CSR describes a type of periodic breathing, where there are cyclical fluctuations in the amplitude of tidal volume, typically in a gradual crescendo-decrescendo pattern interspersed with periods of central apnea (see figure 1.3).(29) SDB reflects a spectrum and may be asymptomatic or lead to significant morbidity and mortality. Severity can be defined clinically e.g. based on sleepiness or on pathophysiological measurements e.g. apnoea-hypopnoea index (AHI) or respiratory disturbance index or by a combination of the two. The term obstructive sleep apnea-hypopnea syndrome (OSAHS) is used where recurrent partial or complete upper

airway obstruction during sleep (OSA) occurs with a specified frequency and is associated with symptoms.(30)

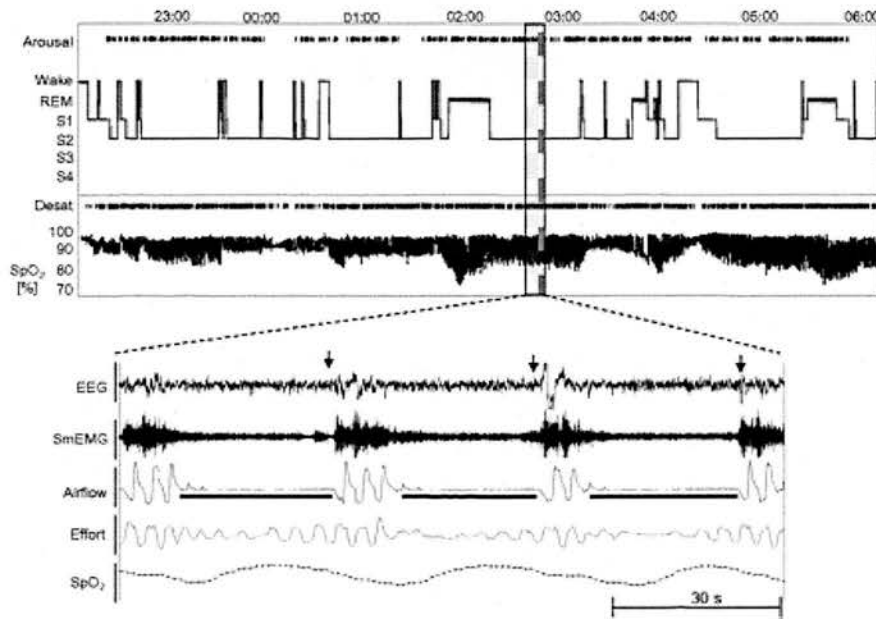
The exact prevalence of SDB is difficult to ascertain due to variations in definitions and diagnostic criteria chosen and also because risk factors for SDB are increasing. The prevalence of SDB in healthy middle-aged adults is estimated to be 4-9%.(31-34) Risk for SDB increases with both age and body mass index.(32;35-37) Racial and genetic influences are also important with increased risk of SDB observed in those with a family history of SDB and also in those with African- American, Asian and Hispanic origin.(38-40) The prevalence of SDB is lower in women than in men, an observation which may be explained in part by hormonal factors.(33;41) Risk in women increases with obesity and also with post-menopausal status.(33;34;42) SDB is more prevalent in smokers than non-smokers and may be exacerbated by factors such as alcohol intake and sedative use.(33;43;44) It is also associated with other medical conditions such as CHF, stroke, hypothyroidism, nasal obstruction and rhinitis, tonsillar and adenoidal enlargement and craniofacial abnormalities.(33;45-49) The Cleveland Family Study has recently reported the incidence of developing SDB, defined by AHI greater than 5 events per hour and by 15 events per hour, to be 7% and 2% per year respectively.(50)

The prevalence of SDB observed in patients with CHF due to left ventricular systolic dysfunction is much higher than in the general population. Early studies reported a prevalence of SDB (AHI > 15 events per hour) of 43 – 82% in patients with stable CHF.(23;29;49;51-54) All but one of these studies reported a predominance of CSA, observed in 29 – 62% of patients with CHF, compared to OSA which was seen in 5 –

32%. However, these studies predate recent advances in CHF therapy which have impacted on morbidity and mortality.(16;17) More recent work has produced conflicting results suggesting a prevalence of SDB between 24 and 71% in this patient population with no consensus on the predominant type of SDB.(55-60) Previously identified risk factors for CSA include age greater than 60 years, male gender, atrial fibrillation and hypocapnia; others report an association between CSA and indices of increased severity of CHF.(23;55-58) Sin *et al* found obesity to be a risk factor for OSA in men with CHF.(23) The reasons for the increased prevalence of OSA in patients with CHF compared to the general population are not well defined, but may in part be due to common risk factors such as obesity and metabolic syndrome.

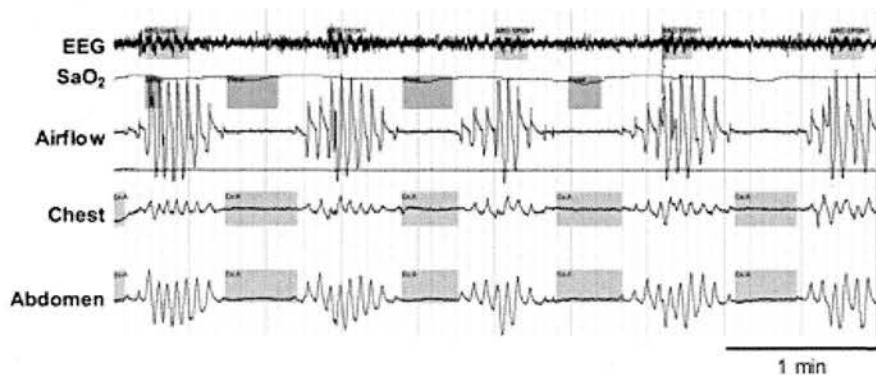
**Figure 1.2(61)**

Sleep hypnogram and oximetry tracing in a patient with severe OSA (AHI 84/hr) and sleep fragmentation. Arrows indicate 3 obstructive apnoeas associated with arousals and oxygen desaturations.



**Figure 1.3(62)**

Example of CSA – CSR: note the crescendo/decrecendo pattern of respiration, absence of chest and abdominal wall movement during apnoeas and arousal at peak of respiratory effort.



## **1.2 PATHOPHYSIOLOGY**

### **1.2.1 Control of ventilation**

The physiological mechanisms controlling ventilation can be loosely divided into metabolic, behavioural and wakefulness systems.(63) Metabolic control includes interaction between chemoreceptors, intrapulmonary vagally-mediated receptors and brainstem mechanisms and matches ventilation to current metabolic and homeostatic requirements. Behavioural control involves neural input from the forebrain and the wakefulness system describes the increased ventilation observed whilst awake. During sleep, however, ventilation is almost solely controlled by the metabolic system. Arterial  $p\text{CO}_2$  plays a key role in maintaining stable and rhythmic ventilation during sleep.(64) There is a linear relationship between increasing  $p\text{CO}_2$  and ventilation. This ensures that only a small rise in  $p\text{CO}_2$  is required to stimulate increased ventilation. In contrast the relationship between arterial  $p\text{O}_2$  and ventilation is a hyperbolic one and as such relatively large changes in  $p\text{O}_2$  have minimal effect on ventilation. The body's own stores of  $\text{CO}_2$  ensure that large changes in ventilation are needed to alter the  $p\text{CO}_2$  and as such this provides a damped and stable feedback system.

### **1.2.2 Obstructive sleep apnoea**

Patency of the upper airway is maintained by a dynamic combination of activity of the surrounding muscles and negative intra-luminal pressure. Abnormalities in upper airway anatomy and neuromuscular control by the higher nervous system may lead to a narrowed and more collapsible pharyngeal airway. Sleep is associated with reduction in pharyngeal muscle tone further predisposing to upper airway obstruction.(65) Obesity



decreases upper airway size as a result of increased deposition of adipose tissue in the surrounding structures and also greater airway collapsibility due to increased muscle mass.(66-70) Patients with CHF may develop increased pharyngeal oedema associated with supine posture during sleep which may further contribute to narrowing of the upper airway.(71;72)

Repeated inspiration against the occluded upper airway generates exaggerated negative intra-thoracic pressure, increased systolic trans-mural pressure, increased left ventricular afterload and reduced stroke volume and cardiac output. The exaggerated negative intra-thoracic pressure also causes increased venous return and right ventricular overload further impairing left ventricular filling.(73;74) In addition, there is repetitive hypoxia, hypercapnia, arousals from sleep, surges in sympathetic activity and loss of vagal heart rate regulation (figure 1.4). Consequently, OSA is associated with systemic hypertension, vascular endothelial dysfunction, increased sympathetic nervous system activity, increased concentrations of inflammatory mediators, increased insulin resistance and cardiac arrhythmias, factors which may all contribute to the progression of CHF.(75-82)

### **1.2.3 Central sleep apnoea**

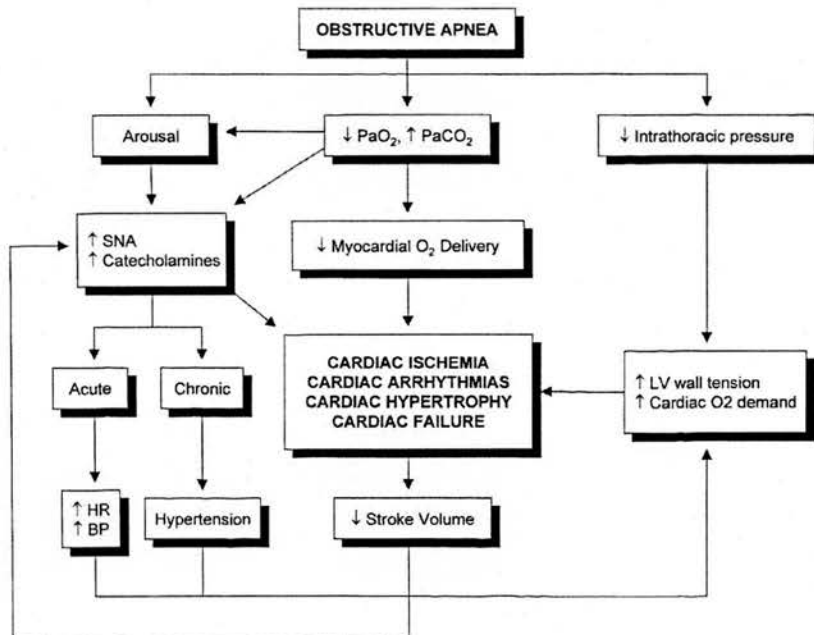
Instability of ventilatory control is implicated in the development of CSA and CSR. Patients with CHF have increased circulation time, increased ventilatory responsiveness to  $p\text{CO}_2$  and reduced functional residual capacity, factors which are all implicated in the development of periodic breathing.(83-85) Increased circulation time leads to delay in transfer of information from pulmonary capillaries to the chemoreceptors regarding

changes in CO<sub>2</sub> and O<sub>2</sub> arterial tension. Lung-to-chemoreceptor circulation time and CSR cycle length have been shown to correlate in patients with CHF.(86) In patients with increased chemoreceptor sensitivity to CO<sub>2</sub>, small increase stimulates hyperventilation. Consequentially, pCO<sub>2</sub> falls below the apnoea threshold and central apnoea ensues until pCO<sub>2</sub> rises again to the level required to stimulate hyperventilation thus maintaining the cycle of periodic breathing.(87-92) Hypoxaemia in CCF is generally mild and therefore not of the severity to cause hyperventilation. Reduced functional capacity introduces 'underdamping' within the control system.(83;84) Changes in pCO<sub>2</sub> and pO<sub>2</sub> are augmented for any given change in ventilation. Functional capacity in patients with CHF may be reduced by cardiomegaly, pleural effusions and decreased respiratory system compliance.

CSA shares many of the pathophysiological effects of OSA with recurrent nocturnal hypoxia, excessive arousals, shift to light sleep stages and activation of the sympathetic nervous system but differs in that there is no generation of exaggerated negative intrathoracic pressure (figure 1.5).(93) However, it is now recognised that patients with CHF may display both central and obstructive apnoeas, which may vary between nights and with treatment.(94;95)

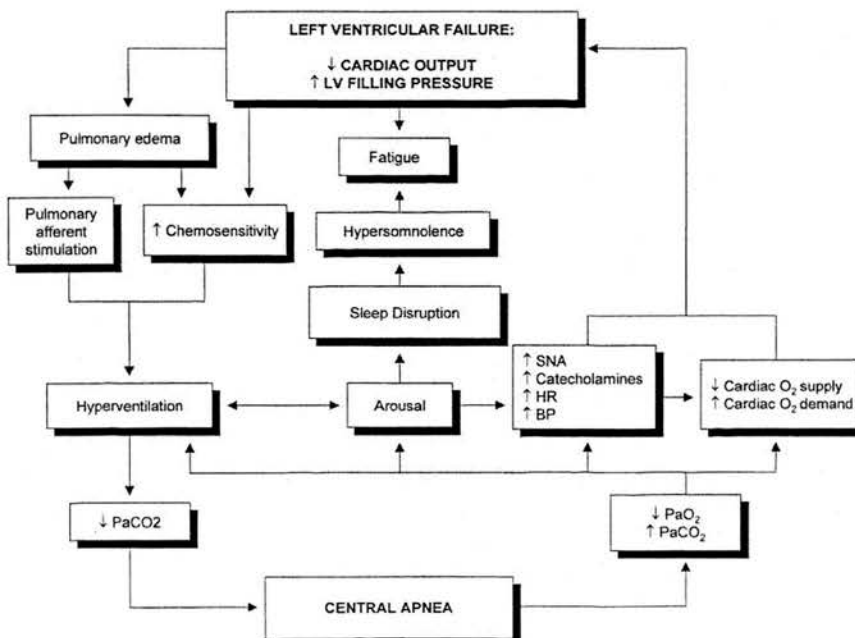
**Figure 1.4(96)**

Pathophysiological scheme of OSA in CHF



**Figure 1.5(96)**

Pathophysiological scheme of CSA in CHF



### **1.3 CLINICAL RELEVANCE OF SLEEP-DISORDERED BREATHING IN CHRONIC HEART FAILURE**

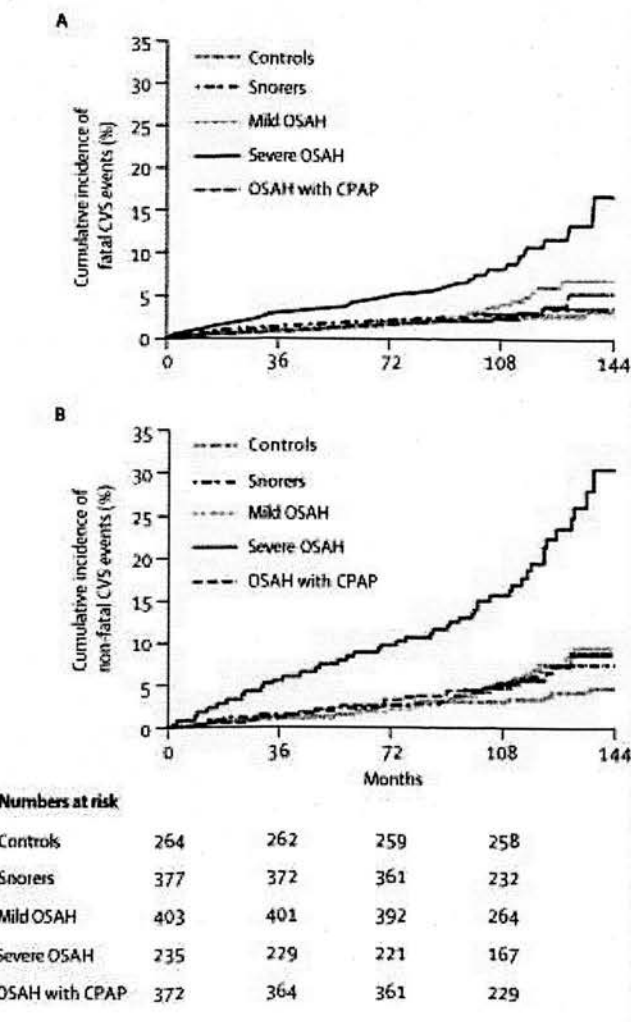
SDB contributes to both morbidity and mortality in patients with CHF. Patients with SDB may complain of fatigue, daytime sleepiness, morning headache, poor concentration, insomnia, nocturnal angina and nocturia. Snoring and abnormal breathing patterns may be witnessed by bed partners. However, it can be seen that there is considerable overlap between the symptoms of SDB and those of CHF, and it is likely that this contributes both to under-reporting and under-diagnosis of SDB in these patients.

#### **1.3.1 Obstructive Sleep Apnoea**

There is increasing evidence that OSA is an independent risk factor for fatal and non-fatal cardiovascular events.(97-102) Marin *et al* reported 2.9 and 3.2 fold higher rate of fatal and non-fatal cardiovascular events respectively in those with severe untreated OSA compared to healthy subjects, after controlling for confounding variables.(97) The cross-sectional Sleep Heart Health Study showed that OSA increased the odds of having CHF by 2.2 fold compared to those without OSA.(98) Furthermore, specifically in patients with CHF, untreated OSA is associated with an increased risk of death independent of other confounding factors (see figures 1.5 and 1.6).(103)

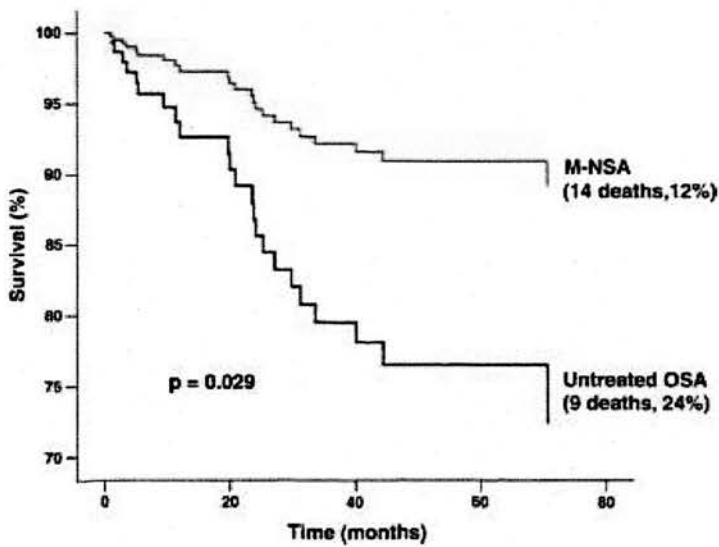
Figure 1.6(97)

Cumulative percentage of individuals with new fatal (A) and non-fatal (B) cardiovascular events in each of the five groups studied



**Figure 1.7(103)**

Multivariable Cox proportional hazards plots showing worse survival of heart failure patients with untreated obstructive sleep apnea (OSA) than in those with mild to no sleep apnea (M-NSA) (hazard ratio = 2.81,  $p = 0.029$ ) after adjusting for significant confounders (left ventricular ejection fraction, New York Heart Association functional class, and age).



### **1.3.2 Central Sleep Apnoea**

Several studies have shown that CSA is a risk factor for increased mortality in patients with CHF.(51;104-108) However, these studies predate recent advances in drug and device therapy for CHF. Indeed a fall in the combined rate of heart transplantation and mortality in patients with CHF and CSA was observed during the course of the Canadian Continuous Positive Airway Pressure for Treatment of Central Sleep Apnea in Heart Failure (CANPAP) trial and was associated with increasing use of beta-blockers, which inhibit excessive sympathetic nervous system activity.(109) Subsequently, patients with CHF receiving interventions of proven benefit in CHF such as beta-blocker and cardiac resynchronisation therapy have been shown to have lower prevalence and severity of CSA.(110;111) Furthermore, CSA is associated with markers of increased severity of CHF and its presence may simply be an indicator of elevated left ventricular filling pressures and decompensated CHF which confer poorer prognosis.(55-58)

## **1.4 DIAGNOSIS OF SLEEP-DISORDERED BREATHING IN PATIENTS WITH CHRONIC HEART FAILURE**

### **1.4.1 Diagnostic Criteria**

The diagnosis and classification of SDB are based on a combination of symptoms and signs and the findings of nocturnal sleep studies. Symptoms may be assessed by direct questioning and completion of sleep-specific questionnaires by the patient and their partner. Symptoms include excessive daytime sleepiness not explained by other factors, nocturnal choking or gasping, recurrent nocturnal arousals or awakenings, unrefreshing sleep and impaired concentration. The AHI, determined by PSG, is used primarily to quantify SDB and respiratory events are classified as obstructive, central or mixed in aetiology. Five, or more, respiratory events per hour of sleep are regarded to be significant.(30) There is currently no clear consensus in some aspects of respiratory event scoring, most notably regarding the definition of a hypopnoea.(112)

### **1.4.2 Sleep Studies**

The American Academy of Sleep Medicine Task Force recognises four levels of sleep study.(30) A level I study involves complete attended overnight PSG performed in the sleep laboratory. This enables determination of sleep and wake states, sleep stages and disturbance, AHI and detection of sleep pathology unrelated to SDB. A level II study also consists of complete PSG but differs in that it is unattended and performed in the home setting. Level III studies involve the use of portable limited systems and can also be used in the home. These record nasal or oral airflow, respiratory movement, oximetry, pulse rate and sleep position but provide no information regarding wake and



sleep states or sleep stages and disturbance. Level IV studies record only pulse rate and oximetry, thus providing very limited information.

A level I study is considered generally to be the gold standard in the diagnosis and classification of SDB. However, PSG is relatively expensive, not widely available and demand exceeds supply, at a time when only a minority of patients with CHF is investigated for SDB.(113) Level III studies have been shown to be useful and cost-effective in the diagnosis of OSAHS. However they have not been validated in patients with CHF and therefore no guidance exists for their use in this specific patient population.(114-119) Level IV studies are not recommended for the diagnosis and classification of SDB but have a role as a screening tool for OSAHS in the adult population.

## **1.5 TREATMENT OF SLEEP-DISORDERED BREATHING IN PATIENTS WITH CHRONIC HEART FAILURE**

### **1.5.1 Continuous Positive Airway Pressure**

Nocturnal CPAP is a well established treatment for OSAHS which improves daytime sleepiness, quality of life, cognitive function, impotence, road traffic accidents, hypertension and other cardiovascular disease, and mortality.(76;97;120-130) CPAP is applied via a nasal or oronasal mask, typically with pressure range 5-15 cm H<sub>2</sub>O. It splints open the entire airway preventing upper airway collapse and increases functional residual capacity. Recently, auto-titrating CPAP has become available.(131;132) This device automatically adjusts pressure according to upper airway obstruction, avoiding many of the disadvantages of titration and treatment with conventional CPAP. It is as effective as fixed pressure CPAP in reducing daytime sleepiness and AHI, increases nightly use and provides better quality sleep and less discomfort.(133;134)

Potential side-effects of CPAP therapy include mask discomfort, claustrophobia, nasal congestion, rhinorrhoea, epistaxis and conjunctivitis. Most of these can be minimised by good mask fitting, patient education, air humidification and possibly nasal decongestants.(135;136) These factors may contribute to problems with compliance, especially in the longer term; indeed, only 50-60% patients may comply with therapy.(137-139) Previous work in patients with OSAHS has shown that there is a need to derive symptomatic benefit from CPAP in order to accept the associated discomfort and inconvenience.(140) Auto-titrating devices may produce better compliance rates due to lower pressure use.

#### **1.5.1.1 Obstructive Sleep Apnoea**

Nocturnal CPAP alleviates acute OSA and reduces nocturnal heart rate, blood pressure and left ventricular afterload.(74;141) Medium term use in patients with OSA and CHF reduces AHI and improves quality of life and cardiovascular function.(142-144) These studies employed parallel group comparisons with small numbers of patients (n=12-19 per group) and no placebo control.(142;144) Absolute increases in left ventricular ejection fraction (LVEF) of 5-12% were reported with 1-3 month use of nocturnal CPAP. Mean CPAP usage varied between 5.6 and 6.2 hours per night. Reductions in daytime blood pressure, sympathetic nervous system activation and ventricular ectopy have also been observed.(142;144-146) The long term impact of CPAP on cardiovascular outcomes in patients with OSA and CHF is unknown.

#### **1.5.1.2 Central Sleep Apnoea**

In patients with CSA and CHF, CPAP increases intra-thoracic pressure, reduces left ventricular transmural pressure and afterload, and reduces left ventricular preload, all of which contribute to a more favourable haemodynamic profile.(53;147) When applied with sufficient pressure for a period of 2-12 weeks, CPAP reduces central AHI.(109;147-150) CPAP is also associated with improvements in symptoms, inspiratory muscle strength, neurohormonal concentrations, sympathetic nervous system activation, functional mitral regurgitation and LVEF.(106;147;149-153) Sin *et al* reported that patients with CSA and CHF who were compliant with CPAP therapy had a relative risk reduction of 81% (95% CI 26-95%,  $p=0.017$ ) in a combined endpoint of death and cardiac transplantation during a median follow-up period of 2.2 years.(106)

The multi-centre CANPAP trial aimed to investigate the effects of long term CPAP on cardiovascular outcomes in patients with CSA and CHF. It is the largest trial to date of CPAP in patients with CHF involving randomisation of 258 patients.(109) However, the trial was terminated early due to a divergence in survival curves which favoured the control group, lower than expected enrollment and a falling primary event rate, associated with a changing pattern of drug therapy.

The CANPAP trial did show, that CPAP use was associated with sustained improvements (over a minimum of 2 years) in CSA, nocturnal oxygenation, exercise capacity, LVEF and plasma norepinephrine concentrations, although with lesser magnitude than previously observed. However, the finding of early adverse outcomes in the group treated with CPAP is of particular concern, something not identified previously in smaller studies. CPAP-induced increases in intrathoracic pressure usually augment cardiac output acutely in patients with CHF with elevated left ventricular pressures but may reduce it in those with low filling pressures.(154) This is one potential haemodynamic mechanism whereby CPAP may have deleterious effects in some patients with CHF and CSA. This possibility of early harm does not support the use of CPAP in CHF patients with CSA outside the setting of well-designed randomised controlled trials.

Subsequent *post hoc* analysis of the CANPAP data was performed to test the hypothesis that suppression of CSA to AHI less than 15 events per hour would improve both LVEF and transplant-free survival.(155) This analysis showed that, compared with control subjects, increases in LVEF and transplant-free survival were greater in the CSA-

suppressed group. However, concerns regarding this interpretation include differences in the baseline characteristics between the untreated controls and both CPAP-treated groups, as well as the inherent problems with *post hoc* analysis.(156)

### **1.5.2 Bi-level and adaptive servo-ventilation**

Other modes of positive airway pressure, namely bi-level pressure support and adaptive servo-ventilation (ASV), have been evaluated in patients with CHF. Bi-level non-invasive ventilation enables differing inspiratory and expiratory pressure support. ASV provides 5cm and 8cm H<sub>2</sub>O expiratory and end-inspiratory pressure respectively during normal breathing but when central apnea is detected it increases end-inspiratory pressure up to a maximum of 15 cm H<sub>2</sub>O to maintain minute ventilation at 90% of the longer-term average ventilation.

Teschler *et al* compared oxygen therapy, CPAP, bi-level pressure support and ASV on consecutive nights in patients with CHF and found significant reductions in CSA with all therapies; however improvements in sleep structure were only observed with ASV.(157) Kohnlein *et al* compared bi-level ventilation to CPAP over a 2 week period in patients with CHF and found similar improvements in daytime sleepiness, sleep quality and CSA but did not assess cardiac function.(148) Pepperell *et al* conducted a randomized controlled trial of therapeutic and sub-therapeutic ASV in patients with CHF and CSA and reported improvements in daytime sleepiness, urinary metanephrine and plasma BNP concentrations, but not in LVEF.(158) These findings contrast with the results from another study comparing ASV and CPAP which showed improvements in LVEF in the group treated with ASV.(159)

### **1.5.3 Other treatment modalities**

Modification of lifestyle factors may be beneficial in reducing SDB.(160) Patients should be advised regarding weight reduction, if obese, and also regarding smoking and alcohol cessation. Sedative drugs should be avoided if possible. Optimisation of CHF therapy may itself reduce CSA.(53;111;161;162) Nocturnal supplemental oxygen therapy has been shown to reduce central AHI and possibly nocturnal sympathetic activity but current data do not suggest improvements in either symptoms or cardiac function.(149;163-166) Furthermore, hyperoxia may have adverse physiological effects.(167;168) Respiratory stimulants, such as theophylline and acetazolamide, have also been shown to reduce central AHI but both have potentially adverse side-effects.(169-171)

## 1.6 HYPOTHESES

SDB in patients with CHF often passes unrecognized and yet is associated with increased morbidity and mortality, and presents a potential therapeutic target.(51;107) Early studies have reported that SDB is highly prevalent in patients with CHF, with a predominance of CSA rather than OSA.(23;49;52) However, these data predate recent important advances in drug and device therapy, which have improved morbidity and mortality, and are now widely adopted in guidelines for the optimal management of patients with CHF.(1;7;15-17)

The symptoms of SDB and CHF overlap and, as such, the diagnosis of SDB is reliant on accurate sleep study measurements. Portable limited sleep study systems, which do not record an electroencephalogram and are applied by patients at home, are a more accessible alternative to full polysomnography (PSG).(113;114) They have been well-validated against PSG in the investigation of OSAHS in the general population but there are few data specifically in patients with CHF.(30;114;119;172;173)

There have been only two previous randomized controlled trials to assess CPAP in patients with CHF and OSA.(142;144) These trials reported that CPAP therapy improved symptoms, LVEF and systolic blood pressure. However, these studies had important limitations including the single blind design, the small numbers of patients (n=12-19 per intervention group) completing study protocols and findings which were not entirely consistent. The effect of CPAP on cardiovascular outcomes in patients with

CHF and OSA therefore is an extremely important clinical question which remains unanswered.

The following hypotheses will be addressed:

1. The prevalence of SDB in patients with CHF treated with optimal medical therapy according to contemporary guidelines is lower than previously reported and is due to a reduction in CSA.
2. There is good agreement in diagnostic outcome between home limited sleep studies and in-laboratory polysomnography in the identification of SDB in patients with CHF.
3. Treatment of OSA in patients with symptomatic stable CHF by nocturnal auto-titrating CPAP:
  - i. is a tolerable method of adjunctive ventilatory support
  - ii. improves exercise capacity, peak oxygen uptake and LVEF
  - iii. improves New York Heart Association class and quality of life measures
  - iv. reduces plasma catecholamine, N-terminal pro-brain natriuretic peptide and N-terminal pro-atrial natriuretic peptide concentrations



## 1.7 AIMS

The aims of the thesis were:

In patients with stable symptomatic CHF (Chapter 3):

- to determine prospectively the prevalence of SDB in the setting of optimal medical therapy according to contemporary guidelines.
- to investigate the clinical characteristics of patients with SDB compared to those without SDB.

In patients with stable symptomatic CHF (Chapter 4):

- to assess the accuracy and clinical utility of a limited sleep study system performed at home, compared with in-laboratory polysomnography, for diagnosing SDB.

In patients with stable symptomatic CHF and OSA (Chapter 5):

- to determine whether, by randomized controlled crossover trial, treatment of OSA by nocturnal auto-titrating CPAP would improve subjective and objective measures of CHF severity.
- to assess the tolerability of nocturnal CPAP therapy.

## **CHAPTER 2**

### **METHODOLOGY**

## **2.1 GENERAL**

### **2.1.1 Ethical considerations**

All studies were undertaken in accordance with the Declaration of Helsinki of the World Medical Association and with the approval of the Lothian and North Glasgow NHS Trust Research Ethics Committees.

All patients participated in these research studies voluntarily. They were all deemed competent to consent and able to consider fully and rationally the implications of taking part. They were provided with adequate information in the form of a detailed patient information sheet and also given the opportunity to discuss further both with trial investigators and also an independent advisor. The written informed consent of each patient was obtained before entry into the study, after a period of more than 24 hours of consideration. Participants were able to withdraw consent at any time without hindrance or detriment to their future treatment. Measures were taken to safeguard patient confidentiality. The use of identifiable information was minimised and data anonymised wherever possible. Research records, both paper and electronic, and anonymously labeled specimens were stored in a secure manner only accessible to authorised personnel. Confidential information was used only for the purpose it was obtained and no individual was identifiable from published results.

### **2.1.2 Subject recruitment**

Patients were recruited from general cardiology clinics at two university hospitals in Edinburgh and from a specialist heart failure clinic in Glasgow. Consecutive patients

aged between 18 and 80 years with symptomatic (NYHA class II-IV) but stable CHF for at least one month on optimal medical therapy and objective evidence of left ventricular systolic dysfunction (echocardiographic LVEF < 45%) were enrolled prospectively. Furthermore, to be eligible for inclusion in the randomised placebo-controlled trial of auto-titrating CPAP in patients with CHF and OSA, they had to also have an AHI  $\geq 15$  (predominantly obstructive) on PSG. Exclusion criteria were acute coronary syndrome within the preceding three months, implantation of a pacemaker or defibrillator within the preceding six months, primary valvular heart disease, sustained ventricular arrhythmias (but not atrial fibrillation) and stroke with residual neurological deficit. Patients who had undergone recent implantation of a cardiac pacemaker or defibrillator were excluded because of concerns that this might independently affect trial endpoints.

Nine patients participated in both the evaluation of a portable limited sleep study system in the diagnosis of SDB (Chapter 3) and the randomised controlled trial of CPAP in OSA (Chapter 5). All of the patients enrolled in these two studies participated in the prospective evaluation of the contemporary prevalence and type of SDB in patients with CHF (Chapter 4).

### **2.1.3 Considerations of study design**

The intervention trial was designed in a randomised double-blind placebo-controlled crossover format to enable patients to act as their own control, thus reducing between-subject variability, avoiding the need for matched control subjects and increasing statistical power.

#### **2.1.4 Randomisation**

Randomisation to treatment order, where indicated, was performed following baseline assessment using sealed envelopes and a balanced block design.

#### **2.1.5 Blinding**

Investigators blinded to intervention modality undertook all measurements and analyses. Specifically, they were not involved in randomisation, device education or follow-up, and study participants were requested not to discuss their device therapy with them.

## **2.2 SLEEP STUDIES**

### **2.2.1 Limited sleep studies**

Limited sleep studies were performed using a commercially available system (Embletta; Flaga, Iceland) measuring: 1) nasal pressure using a nasal cannula/pressure transducer system (recording the square root of pressure as an index of flow), 2) thoraco-abdominal movement from two piezoelectric belts, 3) finger pulse oximetry and 4) body position. Patients were educated in the application of the Embletta device prior to the study and applied the device themselves at home. They were provided with written instructions and a night-time telephone number to call in the event of difficulties. Patients required sufficient agility to apply the thoraco-abdominal bands, nasal cannula and pulse oximeter and connect a single connector to the recording device. No calibration was required.

### **2.2.2 Polysomnography**

Polysomnography was performed following our standard laboratory protocol with a computerised recording system (Compumedics, Abbotsford, Australia) consisting of: 1) sleep monitoring through electro-encephalogram, electro-oculogram, and submental plus outer canthi electromyogram, 2) bilateral tibial electromyogram and body position detector, 3) nasal pressure using a nasal cannula/pressure transducer system, 4) thoraco-abdominal movement from two inductance plethysmographic belts, 5) finger pulse oximetry, 6) snoring detection by digital microphone and 7) three-lead electrocardiogram.(172)

### **2.2.3 Oxford SLEep Resistance test**

During the Oxford SLEep Resistance (OSLER) test, the subject is placed semi-recumbent in a dark and quiet environment and requested to remain awake for a maximum testing time of 40 minutes.(174-176) The presence of sleep is assessed behaviourally. Subjects are asked to touch a non-recoil button (Stowood Scientific Instruments, Oxford, U.K.) each time a light flashes on a socket placed in front at eye level at a distance of 2 metres. The light flashes regularly for 1 second every 3 seconds. The LED and hand response device are relayed to a computer in an adjacent room. The test is terminated after seven consecutive flashes without response, assuming that the subject has been asleep. The OSLER test has been successfully validated against the maintenance of wakefulness test in the evaluation of objective daytime sleepiness.(175;176) The initial description of the test describes repetition of each session four times at two hourly intervals with the overall result calculated as the mean of all four sessions. However, we elected to perform an abbreviated OSLER test repeating each session twice (commencing at 9 and 11 am) after a normal sleep night and abstinence from caffeine or other wakefulness stimulants. Reducing the number of testing sessions has previously been shown not to significantly affect the overall result.(176)

### **2.2.4 Data analysis**

All sleep studies were scored according to standard criteria by the same experienced sleep technician.(177) PSG enables two states of sleep, NREM and REM sleep, and four stages within NREM sleep to be determined. Stage 1 is light sleep occurring at sleep onset and transitions during the night. Stage 2 is defined by sleep spindles and K

complexes in the EEG. Stages 3 (20-50%) and 4 (>50%) are characterized by high-voltage slow waves in EEG and are known as slow-wave sleep. REM sleep is distinguished by relatively low voltage mixed frequency EEG, bursts of rapid eye movements in the EOG and suppression of EMG activity.

A summary of definitions of respiratory events and indices is presented in Table 2.2. Currently several definitions are in use and there is a lack of consensus. In accordance with our current research and clinical practice, apnoeas were defined as a complete cessation in airflow lasting  $\geq 10$  s, and hypopnoeas as a reduction in airflow or thoraco-abdominal movement by  $\geq 50\%$  for  $\geq 10$  s. Apnoeas were classified as 1) *obstructive* if thoraco-abdominal movement was present during the apnoea; 2) *central* if thoraco-abdominal movement was absent; and 3) *mixed* if thoraco-abdominal movements were both present and absent during the period of airflow cessation. (30) We used the American Academy of Sleep Medicine definition of significant respiratory events which does not require oxygen desaturation when flow is measured by nasal pressure rather than thermal signal.(30) Flow was recorded by nasal pressure in addition to thoraco-abdominal movement and these signals were used to identify hypopnoeas. Hypopnoeas cannot be differentiated with certainty between central or obstructive from surface techniques and therefore events per hour are reported rather than central and obstructive events separately.

The Embletta device does not record sleep and therefore only an apnoea/hypopnoea measure per hour in bed, rather than an AHI, can be calculated. For Embletta studies performed at home, analysis was started once respiration settled to a stable rhythmic



pattern and stopped either according to the time of awakening as provided by the patient or based on tracing quality and breathing pattern. The start and end of the laboratory Embletta analysis were set according to the start and end time of the synchronous PSG. For the synchronous PSG studies, both AHI and apnoea/hypopnoea measure per hour in bed were calculated to enable direct comparison of techniques.

**Table 2.1**

Definitions of Respiratory Events and Indices

<b>Respiratory event</b>	<b>Definition</b>
Apnoea	Complete cessation of airflow $\geq 10$ seconds.
Hypopnoea	Reduction in airflow or thoraco-abdominal movement by $\geq 50\%$ for $\geq 10$ seconds. Several definitions are in use (including need for association with EEG arousal or oxygen desaturation) & there is currently a lack of consensus.
RERA	Sequence of breaths with increasing respiratory effort leading to an arousal as shown by increasingly negative oesophageal pressure for $\geq 10$ seconds preceding an arousal with resumption of more normal pressures. A clinical definition has not been agreed on.
<b>Type of respiratory event</b>	
Obstructive	Thoraco-abdominal movement present during event
Central	Thoraco-abdominal movement absent during event
Mixed	Thoraco-abdominal movement both present and absent during event
<b>Indices of SDB</b>	
AHI	Number of apnoeas & hypopnoeas per hour of total sleep time.
Apnea index	Number of apnoeas per hour of total sleep time.
Hypopnoea index	Number of hypopnoeas per hour of total sleep time.
A+H	Number of apnoeas & hypopnoeas per hour in bed.
RERA index	Number of RERAs per hour of total sleep time.
Respiratory disturbance index	Number of apnoeas, hypopnoeas and RERAs per hour of total sleep time.
Oxygen desaturation index	Number of oxygen desaturations $\geq 3-4\%$ per hour of total sleep time.

Adapted from Kushida *et al*, 2005.(178)

## **2.3 NON-INVASIVE VENTILATION**

### **2.3.1 Continuous positive airway pressure**

Auto-titrating CPAP automatically adjusts pressure according to upper airway obstruction. It is as effective as fixed pressure CPAP in reducing daytime sleepiness and AHI and avoids many of the disadvantages of titration and treatment with conventional CPAP.(133;134) Patients underwent an initial daytime education session and were then supervised for their first night on each device in the Sleep Centre. They were asked to use the machine for a minimum of six hours per night at home and provided with a contact telephone number in case of any problems. In addition, all patients were contacted by telephone by the Sleep Centre Research Nurse within 2 weeks of taking each device home. Compliance with therapy was assessed by interrogation of the CPAP unit to provide nightly usage data.

### **2.3.2 Sham continuous positive airway pressure**

Sham CPAP was chosen as the placebo in the interventional study. It was felt important to control for placebo effect as this is a potential source of error. Previous studies with CPAP in OSA have shown placebo effects with both tablets and sham CPAP.(127;140) Failure to control for placebo effect therefore could overestimate differences in endpoints between treatment and non-treatment limbs of the study. There is no perfect placebo for CPAP since the placebo should ideally be indistinguishable from the active treatment for both the investigator and the patient.(179) Sham ventilation is not indistinguishable from assisted ventilation for the patient and this may lead to unblinding, non-compliance and increased drop-out rates. However, unlike a placebo

tablet, it does control for the discomfort and possible sleep disruption of wearing a facial mask overnight and observer blinding is easier to maintain. In addition, a placebo tablet may not be perceived by the patient as a comparable therapy to CPAP thus adding a further source of bias.

Only one of the published trials in chronic heart failure and CPAP has used a placebo control; sham CPAP was generated by setting delivered airway pressure to a minimum and using a nasal mask with a hole drilled in the connector to reduce mask pressure to less than 1.5 cm H<sub>2</sub>O.(180) Whilst only a small study involving 8 patients, the placebo pressure was generally preferred. This strategy is well described in the literature for studies of CPAP in OSA.(125;181-183) A comparison of CPAP versus sham CPAP in OSA encouragingly showed very similar usage rates and no difference in respiratory or neurological variables.(183) Study patients were informed that the two types of breathing device were being compared, that they would receive both in a random order and that it was unclear which was more effective.

The sham device was created by setting delivered airway pressure to a minimum, inserting a flow-restricting connector at the machine outlet, and creating an extra hole in the collar of the main tubing at the end of the mask. The device created a CPAP pressure of ~1 cm H<sub>2</sub>O.

## **2.4 ASSESSMENT OF SEVERITY OF CHRONIC HEART FAILURE**

The parameters chosen to assess severity of CHF all provide important prognostic information, whilst noting that LVEF correlates poorly with symptoms and functional limitation.(184-187) Major treatment advances in the management of CHF, such as the introduction of ACE inhibitors, beta-blockers, and, more recently, cardiac resynchronization therapy, have been shown to improve these parameters and subsequently, in large randomized controlled trials, to reduce hospitalisation rates and mortality.(9;13;15;16)

Study protocols were designed to enable assessments to be performed in the same sequence and under the same testing conditions *i.e.* timing, preparation and environment, enabling consistency of testing both between individual study participant visits and also between different study participants.

### **2.4.1 Quality of life**

Clinical assessment was performed at each study visit and NYHA class recorded. Standardised and well-validated questionnaires (SF-36, Minnesota Living with Heart Failure and Epworth Sleepiness Scale) were used to assess quality of life and symptoms.  
(188)

### **2.4.2 Echocardiography**

Trans-thoracic Doppler echocardiography was performed by a single, experienced research sonographer using an ATL HDI 5000 system (Philips Medical Systems Limited, Stevenage, U.K). Left ventricular volumes and ejection fraction were calculated according to modified Simpson's rule.

### **2.4.3 Exercise testing**

At baseline evaluation, two 6 minute walk and two cardiopulmonary exercise tests were performed on separate days to minimise any potential bias due to a training effect; the second tests were taken as baseline data.

#### **2.4.3.1 Six minute walk**

A standardised test procedure was followed.(189) Patients were asked to walk around a walking track, covering as much distance as possible during 6 minutes, and were allowed to rest if required.

#### **2.4.3.2 Cardiopulmonary exercise testing**

##### **2.4.3.2.1 Technique**

Symptom-limited exercise tests were performed under physician supervision using an electronically-braked cycle ergometer. The incremental exercise protocol was individualised aiming for exercise duration between 8 and 12 minutes.(190) A 12-lead electrocardiogram was monitored continuously during the test and cuff blood pressure was recorded manually every two minutes. Patients were asked to exercise to

exhaustion and all tests were conducted under physician supervision. Criteria for terminating the test early included ischaemic ECG changes, ventricular arrhythmia, hypotension (systolic BP < 90 mmHg), severe hypertension (systolic BP > 220 mmHg) and patient request. Respiratory gas exchange measurements were obtained breath-by-breath using a computerised metabolic cart (MSX, Ferraris Group Plc, Birmingham, U.K). Gas and flow calibrations were performed before each test.

#### **2.4.3.2.2 Data analysis**

Breath-by-breath data were formatted using a rolling eight breath average. Peak  $\text{VO}_2$ ,  $\text{VCO}_2$  and  $\text{VE}$  were recorded as the highest such values within the last 30 seconds of the test. Predicted peak  $\text{VO}_2$  values were calculated using the standard formulae described by Wasserman *et al.*(191) The anaerobic threshold was determined non-invasively using a dual method (V-slope and ventilatory equivalents) approach as the respiratory exchange ratio approximated unity.(192) The  $\text{VE}/\text{VCO}_2$  slope was calculated as a linear regression function, excluding the non-linear part of the relationship after the onset of acidotic drive to ventilation.(190)

#### **2.4.4 Neurohormonal markers**

Venesection was performed after a period of 30 minutes rest in a semi-recumbent position in a quiet room. Blood samples were collected in EDTA with additive trasylol or 2% sodium metbisulphite and spun at 1000 g for 20 minutes at 4°C. The plasma was then extracted and frozen in aliquots at -40 °C until analysis.

#### **2.4.4.1 N-terminal pro-brain and pro-atrial natriuretic peptides**

NT-proBNP and NT-proANP were measured using a chemiluminescent immunoassay (Roche Diagnostics Ltd, Lewes, U.K.) on an Elecsys 2010 analyser.

#### **2.4.4.2 Plasma catecholamines**

Plasma norepinephrine concentrations were determined by an electrochemical method after separation by reverse phase high performance liquid chromatography.(193)



## 2.5 STATISTICAL ANALYSIS

Data were collected and stored in accordance with the Data Protection Act. Statistical analyses were performed using Statistical Package for Social Sciences version 10 (SPSS inc., Chicago, U.S.A) and GraphPad Prism version 4 (GraphPad Software, San Diego, U.S.A.) software. Continuous variables are expressed as mean values ( $\pm$ SD), or when not normally distributed data as medians (interquartile range). Differences were assessed by two-tailed, paired or unpaired, t-tests as appropriate. The Bland and Altman method was used to assess agreement between two methods of clinical measurement.(194) Correlation between two measures was assessed by Pearson's, or where not normally distributed, Spearman's method. NT-proBNP and NT-proANP data were normalised by logarithmic transformation prior to analysis. The randomised placebo-controlled trial of auto-titrating CPAP in patients with CHF and OSA had 80% power, at 5% significance level, to detect absolute differences in primary end-points of 1.1 mL/min/kg in peak  $\text{VO}_2$  and 33m in 6-minute walk distance, assuming standard deviation of expected changes of 1.9 mL/kg/min and 57 m respectively. Statistical significance was taken at the 5% level.

## **CHAPTER 3**

### **DIAGNOSIS OF SLEEP-DISORDERED BREATHING IN PATIENTS WITH CHRONIC HEART FAILURE: EVALUATION OF A PORTABLE LIMITED SLEEP STUDY SYSTEM**

Smith LA, Chong WS, Vennelle M, Denvir MA, Newby DE, Douglas NJ. Diagnosis of Sleep-Disordered Breathing in Patients with Chronic Heart Failure: Evaluation of a Portable Limited Sleep Study System. *J Sleep Res* 2007;16:428-435

### 3.1 SUMMARY

Sleep-disordered breathing is common in CHF, affects disease progression and presents a potential therapeutic target. This study was designed to test the hypothesis that there would be good agreement in diagnostic outcome between home limited sleep studies and in-laboratory PSG in the identification of SDB in patients with CHF. We performed synchronous in-laboratory Embletta and PSG, and home Embletta studies, prospectively in 20 consecutive patients with stable symptomatic CHF (LVEF  $33\pm 12\%$ ) on optimal medical therapy. Sleep efficiency was poor at  $57\pm 21\%$ . Unlike synchronous in-laboratory Embletta (kappa coefficient 0.63,  $p<0.01$ ), home Embletta showed poor agreement with PSG (kappa coefficient 0.27,  $p=0.06$ ). Positive and negative predictive values for home Embletta in detecting SDB were 83% and 57% respectively. In this relatively small study, agreement in diagnostic outcome between home Embletta and PSG, and negative predictive value for the home Embletta, were poor. We explore possible explanations for this, both technical and situational, which should be taken into consideration when considering potential screening or diagnostic tools for SDB in patients with CHF.

### 3.2 INTRODUCTION

Despite recent advances in pharmacological treatment, CHF is a common cause of morbidity and mortality, and is an increasing clinical and economic burden on healthcare systems.(3) CHF is frequently associated with SDB, including both OSA and CSA. The reported prevalence varies according to the population studied and the diagnostic threshold in AHI chosen, but may be as high as 61%.(23;49) OSAHS is associated with systemic hypertension, vascular endothelial dysfunction, increased sympathetic nervous activity and increased levels of inflammatory mediators.(78;80-82) These important factors are all implicated in both the development and progression of CHF. Randomised controlled trials in patients with OSA have shown that CPAP improves cardiac function, sympathetic nervous system activity, quality of life and reduces blood pressure.(142;144) CSA has similar deleterious effects and CSR, a form of CSA, is an independent marker for increased mortality in CHF.(51;107) CPAP, and more recently, adaptive servoventilation, have been shown to improve daytime sleepiness, cardiac function and sympathetic activity.(147;158;163) However, in contrast to previous work, the recently reported CANPAP trial did not demonstrate a beneficial effect of CPAP on morbidity or mortality in patients with CHF and CSA.(106;109)

The symptoms of CHF and SDB overlap, and whilst CHF patients with SDB have objectively measured daytime sleepiness, few patients actually complain of it.(22;49;195) As such, the diagnosis of SDB in CHF patients is reliant on accurate sleep study measurements. Portable limited sleep study systems, which do not record an

electroencephalogram and are applied by patients at home, are a cheaper and more accessible alternative to full PSG.(113;114;119) They have been well-validated against PSG in the investigation of OSAHS in the general population but there are few data published specifically in patients with CHF.(22;30;114;172). This study was designed to test the hypothesis that there would be good agreement in diagnostic outcome between home limited sleep studies and in-laboratory PSG in the identification of sleep-disordered breathing in patients with CHF.

### **3.3 METHODS**

#### **3.3.1 Subjects**

The study cohort consisted of 20 consecutive consenting CHF patients aged between 18 and 80 years recruited from general cardiology out-patient clinics. Patients had a diagnosis of symptomatic (NYHA class II-IV) but stable CHF for at least one month on optimal medical therapy and objective evidence of left ventricular systolic dysfunction (echocardiographic LVEF < 45%). Exclusion criteria were acute coronary syndrome within the preceding three months, primary valvular heart disease and stroke with residual neurological deficit. The study conformed to the principles outlined in the Declaration of Helsinki, the protocol had the approval of the local ethics committee and all patients provided written informed consent.

#### **3.3.2 Sleep study recordings**

The study consisted of two comparisons: 1) synchronous in-laboratory study (PSG versus limited study) and 2) home study (limited study at home versus in-laboratory PSG on two separate nights). Limited studies were performed using a commercially available system (Embletta; Flaga, Iceland). Synchronous in-laboratory Embletta (LE) and PSG, and home Embletta (HE), studies were performed on two separate nights (time interval between studies: median 2, range 1-7 days). The Embletta device measured the following: 1) nasal pressure using a nasal cannula/pressure transducer system (recording the square root of pressure as an index of flow), 2) thoraco-abdominal movement from two piezoelectric belts, 3) finger pulse oximetry and 4) body position (Figure 4.1). Patients were educated in the application of the Embletta device prior to

the home study and applied the device themselves at home. They were provided with written instructions and a night-time telephone number to call in the event of difficulties. Patients required sufficient agility to apply the thoraco-abdominal bands, nasal cannula and pulse oximeter and connect a single connector to the recording device. No calibration was required when the Embletta was applied.

Polysomnography was performed following our standard laboratory protocol with a computerised recording system (Compumedics, Abbotsford, Australia) consisting of: 1) sleep monitoring through electro-encephalogram, electro-oculogram, and submental plus outer canthi electromyogram, 2) bilateral tibial electromyogram and body position detector, 3) nasal pressure using a nasal cannula/pressure transducer system, 4) thoraco-abdominal movement from two inductance plethysmographic belts, 5) finger pulse oximetry, 6) snoring detection by digital microphone and 7) three-lead electrocardiogram.(172)

### **3.3.3 Analysis of sleep study recordings**

All sleep studies were scored according to standard criteria by the same experienced sleep technician who was blinded to the patients' identities.(177) Analysis of recordings was batched to ensure that no comparisons could be made between individual studies.

Apnoeas were defined as a complete cessation in airflow lasting  $\geq 10$ s, and hypopnoeas as a reduction in airflow or thoraco-abdominal movement by  $\geq 50\%$  for  $\geq 10$ s. Apnoeas were classified as 1) *obstructive* if thoraco-abdominal movement was present during the apnoea; 2) *central* if thoraco-abdominal movement was absent; and 3) *mixed* if thoraco-

abdominal movements were both present and absent during the period of airflow cessation.(30)

The in-laboratory PSG yielded two apnoea/hypopnoea measures: 1) an *apnoea/hypopnoea index* (AHI) which was calculated by dividing the total number of apnoeas and hypopnoeas after sleep onset by the total sleep time, and 2) an *apnoea/hypopnoea measure per hour in bed* (A+H) calculated by dividing the total number of apnoeas and hypopnoeas by the number of hours in bed. As the Embletta device does not record sleep, only an apnoea/hypopnoea measure per hour in bed (A+H) was calculated: A+H<sub>LE</sub> for the synchronous laboratory Embletta and A+H<sub>HE</sub> for the home Embletta study. The start and end of the laboratory Embletta analysis were set according to the start and end time of the synchronous PSG thus allowing a direct comparison in techniques. For the home Embletta, analysis was started once respiration settled to a stable rhythmic pattern and stopped either according to the time of awakening as provided by the patient or based on tracing quality and breathing pattern.

Patients were divided into 3 groups on the basis of the Embletta results: no SDB, possible SDB and definite SDB (A+H<10, A+H 10-20, A+H>20 per hour in bed respectively) according to our laboratory protocol for the investigation of OSAHS.(114) This enabled us to assess agreement outcome between the Embletta and laboratory PSG. Patients were diagnosed as having SDB if they had an AHI of  $\geq 15$  on PSG. Patients were then classified as OSA if the apnoeas detected were predominantly obstructive, and CSA if predominantly central. Hypopnoeas were not further classified as this is not possible without invasive measures.



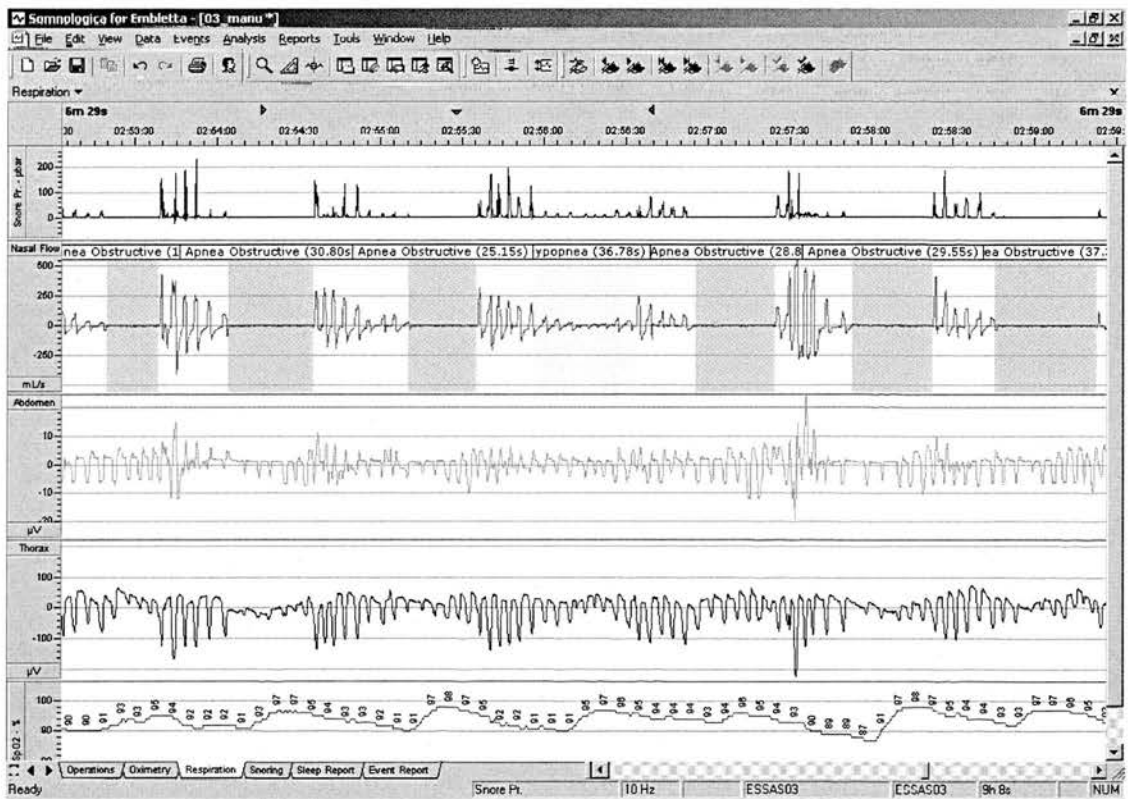
#### **3.3.4 Statistical analysis**

The Bland and Altman method was used to assess agreement between two methods of clinical measurement *i.e.* portable limited study and laboratory PSG, taking into consideration differences in scoring criteria.(194) Correlation between two measures was assessed by Pearson's method. Diagnostic accuracy of patients' classification into 3 groups (no SDB, possible SDB, definite SDB) based on the limited study was assessed by kappa statistics which evaluated outcome agreement between Embletta and laboratory PSG studies. Two-tailed, paired t-tests were used to detect any significant differences between sleep study measurements. Data are presented as mean  $\pm$  standard deviation unless stated otherwise and  $p < 0.05$  was accepted as statistically significant.

**Figure 3.1**

Limited sleep study demonstrating obstructive sleep apnoea/hypopnoea

Continued thoraco-abdominal movement during apnoeas and hypopnoea is associated with oxygen desaturations and snoring and indicates obstructive aetiology (intermittent complete or partial upper airway occlusion). Note the limited sleep study does not record an electroencephalogram and therefore actual sleep time cannot be accurately assessed.



## 3.4 RESULTS

### 3.4.1 Patient Characteristics

Patients (Table 3.1) were typically late middle-aged or elderly with mild to moderate symptomatic CHF (NYHA class 2 or 3) due to LV systolic dysfunction and were on appropriate medical therapy. They were not markedly overweight (BMI  $29 \pm 6$  kg/m<sup>2</sup>) and did not report excessive daytime sleepiness (Epworth score  $8 \pm 4$ ). The study group had a mean sleep efficiency (% time in bed for sleep actually spent asleep) of  $57 \pm 21\%$  and mean total sleep time of  $4.0 \pm 1.6$  hours. Mean AHI was  $26 \pm 22$  and mean central apnoea index  $3 \pm 10$  per hour of sleep. Eleven (55%) patients had an AHI  $>15$  per hour. One patient had CSA and the other 10 patients OSA; only 2 of these patients reported excessive daytime sleepiness (Epworth score  $\geq 11$ ). None of the patients demonstrated Cheyne-Stokes respiration.

### 3.4.2 Recording adequacy

#### 3.4.2.1 In-laboratory studies

A single nasal cannula was used *per* study and divided to provide an input to both PSG and the Embletta. This minimised patient discomfort whilst maintaining adequate nasal pressure tracings. All synchronous PSG and Embletta studies were of acceptable quality.

### **3.4.2.2 Home studies**

Two of the twenty home Embletta studies had intermittently poor nasal pressure traces; however these studies, whilst suboptimal, were interpretable with the combined use of nasal pressure and thoraco-abdominal movement traces. An additional two home studies had no oxygen saturation tracing and one further study was repeated due to patient error.

### **3.4.3 Diagnostic accuracy**

#### **3.4.3.1 Synchronous in-laboratory study – PSG v Embletta (LE)**

Mean A+H per hour in bed measured by PSG was  $24 \pm 17$  compared to  $20 \pm 16$  by synchronous LE (Table 3.2;  $p < 0.01$ ). There was a close correlation between the results of the two studies ( $r = 0.92$ ,  $p < 0.01$ ) and Bland Altman analysis (PSG-LE) showed a mean bias of  $5 \pm 7$ /hr and limits of agreement of -8 to +18/hr (Figure 3.2a). Comparison of LE A+H per hour in bed to PSG AHI per hour slept also showed good correlation and agreement ( $r = 0.94$ ,  $p < 0.01$ ; mean bias  $6 \pm 9$ , limits of agreement -11 to +24) (Figure 3.2b). There was good agreement in outcomes between LE and PSG A+H in the in-laboratory synchronous study (kappa coefficient 0.63,  $p < 0.01$ ). Sensitivity and specificity values for LE were 91% and 89% ( $AHI \geq 15$ ) and 83% and 50% ( $AHI \geq 5$ ) respectively. Positive and negative predictive values were 91% and 89% ( $AHI \geq 15$ ) and 94% and 100% ( $AHI \geq 5$ ) respectively.

#### 3.4.3.2 Home study - PSG v Embletta (HE)

Mean A+H per hour in bed measured by HE was  $14 \pm 13$  compared to  $24 \pm 17$  by PSG on separate nights (Table 3.2;  $p < 0.01$ ). There was reasonable correlation between measures ( $r = 0.54$ ,  $p = 0.01$ ) with mean bias (PSG-HE) of  $10 \pm 15$ /hr and limits of agreement of -18 to +39/hr (Figure 3.2c). Further comparison of the HE A+H per hour in bed to the PSG AHI per hour slept revealed a mean bias of  $12 \pm 19$  and limits of agreement of -25 to +49 (Figure 3.2d). Differences between measures were more likely to occur at higher event rates and therefore, when measures  $\geq 40$  per hour were excluded, there appeared to be greater agreement (A+H (PSG-HE):  $9 \pm 8$ , PSG AHI - HE A+H:  $7 \pm 8$ ).

Ten of the twenty patients had a HE A+H per hour in bed  $< 10$ , of whom 5 had PSG AHI  $< 15$  and 5 had AHI  $\geq 15$  per hour slept. Six patients had a HE A+H per hour in bed in the range of 10-20, and of these 2 had AHI  $< 15$  and 4 had AHI  $\geq 15$  on PSG. Of the 4 patients with HE A+H of  $\geq 20$  per hour in bed, all but one had AHI  $\geq 15$  on PSG; in this one patient most events occurred during awake time which could not be determined from the Embletta study. However, agreement in outcomes between HE and PSG AHI was poor (kappa coefficient 0.27,  $p = 0.06$ ). Sensitivity and specificity values for HE were 45% and 89% (AHI  $\geq 15$ ) and 83% and 50% (AHI  $\geq 5$ ) respectively. Positive and negative predictive values were 83% and 57% (AHI  $\geq 15$ ) and 99% and 25% (AHI  $\geq 5$ ) respectively.

The percentage of the night spent supine was higher on the in-laboratory compared to the home night as determined by the Embletta device [median (IQR) LE 49 (25,99)%, HE 26 (11,42)%], as was the mean A+H per hour in bed (LE  $20 \pm 16$ , HE  $14 \pm 13$ ). Supine

A+H was  $24\pm 21$  and  $22\pm 19$  per hour in bed ( $p=0.81$ ), and non-supine A+H  $12\pm 14$  and  $22\pm 18$  per hour in bed ( $p=0.12$ ), for the home and in-laboratory Embletta studies respectively. Although not used in the definition of respiratory events, 4% desaturation frequencies varied between devices and were lower ( $p=0.04$ ) with PSG than with simultaneous LE but no different between HE and either in-laboratory recording ( $p>0.25$ ) (Table 3.2).

**Table 3.1**

Study patient characteristics

<b>Patient characteristic</b>	<b>Mean <math>\pm</math> SD</b>
Age (years)	61 $\pm$ 10
Sex (male:female)	14:6
Body mass index (kg/m <sup>2</sup> )	29 $\pm$ 6
Aetiology of CHF	
Ischaemic heart disease	13 (65%)
Dilated cardiomyopathy	7 (35%)
Atrial fibrillation	3 (15%)
Left ventricular ejection fraction (%)	33 $\pm$ 12
Drug treatment	
ACE inhibitors / ARBs	18 (90%)
Beta blockers	14 (70%)
Digoxin	6 (30%)
Diuretics	14 (70%)
Spironolactone	6 (30%)
NYHA class	2.3 $\pm$ 0.6
Epworth sleepiness score	8 $\pm$ 4
PSG measurements	
AHI	26 $\pm$ 22
Total sleep time (hours)	4.0 $\pm$ 1.6
Sleep efficiency (%)	57 $\pm$ 21
Oxygen saturation (%)	93 $\pm$ 3

ACE: angiotensin converting enzyme, ARB: angiotensin receptor blocker

**Table 3.2**

Sleep study data

Sleep study measurement	Home Embletta	Lab	PSG*
		Embletta Mean $\pm$ SD	
Obstructive apnoeas	22.6 $\pm$ 36.3	33.9 $\pm$ 64.5	26.7 $\pm$ 62.5
Obstructive apnoeas per hour	2.9 $\pm$ 5.1	4.5 $\pm$ 8.1	6.3 $\pm$ 13.4
Central apnoeas	1.8 $\pm$ 5.0	4.4 $\pm$ 14.4	11.2 $\pm$ 35.4
Central apnoeas per hour	0.2 $\pm$ 0.6	0.6 $\pm$ 1.8	2.8 $\pm$ 9.6
Mixed apnoeas	0.0 $\pm$ 0.0	0.3 $\pm$ 0.9	0.1 $\pm$ 0.2
Mixed apnoeas per hour	0.0 $\pm$ 0.0	0.0 $\pm$ 0.1	0.0 $\pm$ 0.0
Hypopnoeas	87.7 $\pm$ 78.0	104.2 $\pm$ 10.0	60.9 $\pm$ 47.8
Hypopnoeas per hour	10.6 $\pm$ 8.9	14.4 $\pm$ 10.0	16.4 $\pm$ 13.5
Total apnoeas + hypopnoeas	112.1 $\pm$ 103.4	142.7 $\pm$ 122.3	98.8 $\pm$ 93.1
Apnoea + hypopnoeas per hour in bed (A+H)	13.7 $\pm$ 12.6	19.5 $\pm$ 16.0	24.2 $\pm$ 16.8
Apnoea hypopnoea index (AHI)	-	-	25.7 $\pm$ 22.2
Total time in bed (Embletta) / asleep (PSG) (hours)	8.2 $\pm$ 1.4	7.3 $\pm$ 0.8	4.0 $\pm$ 1.6
Sleep efficiency (%)	-	-	57 $\pm$ 21
Oxygen saturation (%)	94 $\pm$ 2	93 $\pm$ 3	93 $\pm$ 3
Oxygen desaturations $\geq$ 4% per hour	7.5 $\pm$ 7.1	14.9 $\pm$ 15.4	4.8 $\pm$ 6.9

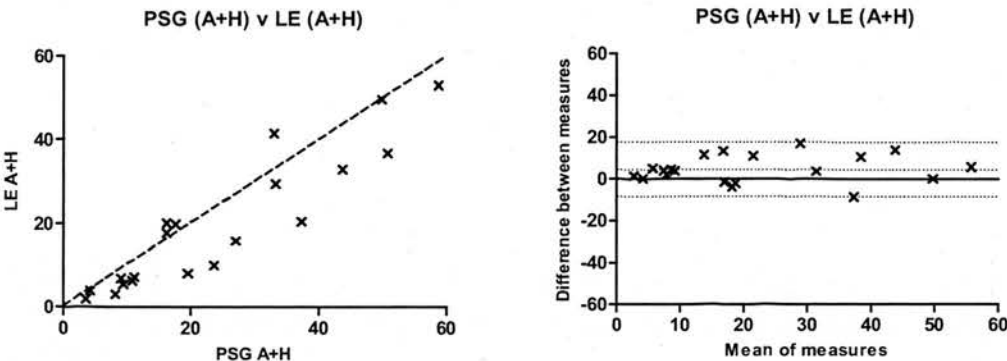
\*Events recorded during sleep unless otherwise stated.



**Figures 3.2a-d**

Scatter plots (left) with lines of equality. Bland Altman plots (right) where the middle dotted line represents the mean bias and the outer dotted lines represent the 95% limits of agreement. PSG: polysomnography, LE: in-laboratory Embletta, HE: home Embletta, A+H: apnoeas + hypopnoeas per hour in bed, AHI: apnoea/hypopnoea index per hour slept.

**Figure 3.2a**



**Figure 3.2b**

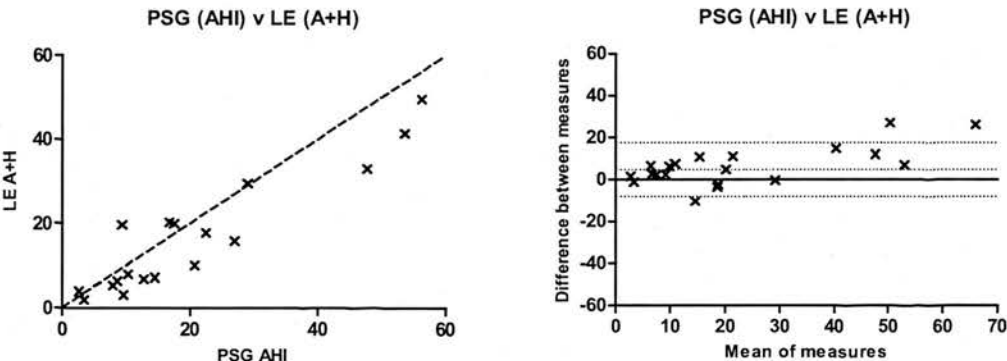


Figure 3.2c

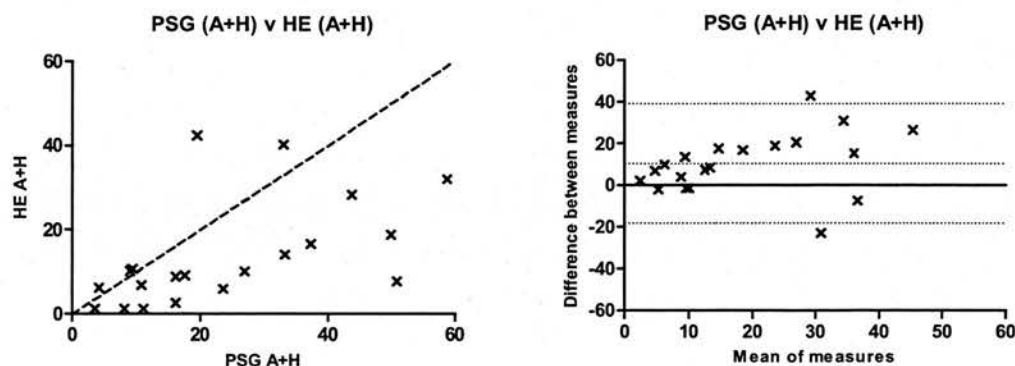
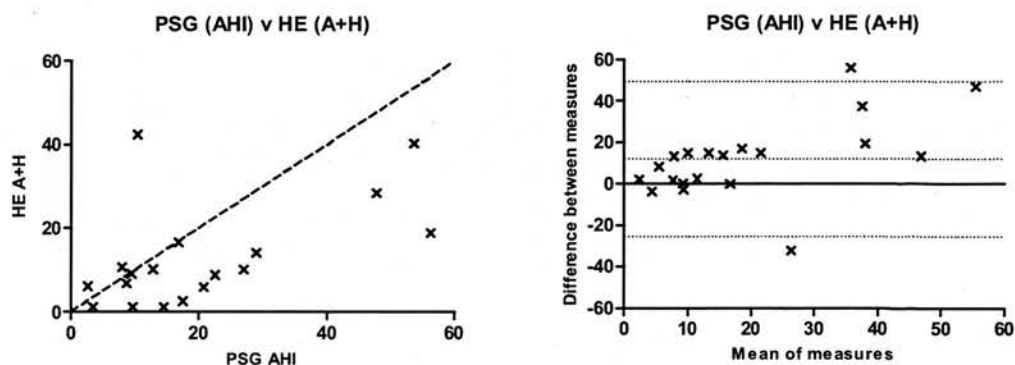


Figure 3.2d



### 3.5 DISCUSSION

This is the first study to evaluate the use of a portable limited sleep study system, performing both synchronous in-laboratory (PSG v limited) and home studies, in the diagnosis of SDB specifically in patients with CHF. Agreements in diagnostic outcome between home Embletta and PSG, and negative predictive value for the home Embletta, were poor. We explore possible explanations for this, both technical and situational, which need to be taken into consideration, particularly when investigating patients with CHF.

There is currently no accepted, widely available screening tool for SDB in CHF patients. This is despite an increasing body of evidence demonstrating the importance of the co-existence of SDB and CHF, and the potential treatment benefits of non-invasive ventilation. PSG is relatively expensive, not widely available and demand already exceeds supply, at a time when only a minority of patients with CHF are investigated and treated for SDB. Furthermore, there is considerable overlap between symptoms of CHF and SDB. It is therefore difficult to see how the yield on PSG can be increased if we are unable to predict clinically which patients are likely to have SDB. In addition, there may be significant cardiovascular benefits to be gained by treatment, even in the absence of symptoms of SDB.

Portable limited sleep study systems have been shown to be both useful and cost-effective in the diagnosis of OSAHS,(114-117;119;196) and may therefore be of value in the diagnosis of SDB in CHF patients.(197) In this study, the Embletta performed

well compared to PSG when examined under identical patient and environmental conditions. However, it compared less well when tested in the home setting, for which it was specifically designed and in which it is almost exclusively used in clinical practice. It provided some useful information, in that a positive result was very likely to reflect a positive PSG result; however a negative result did not exclude the diagnosis of SDB and therefore further investigation by PSG would be required. Overall, agreement in diagnostic outcome between home Embletta and PSG, and the negative predictive value of the Embletta, were poor.

Possible explanations for this poor agreement can be due to both technical *i.e.* Embletta vs PSG and situational *i.e.* home vs in-laboratory differences. It is important to recognize the differences between the measures obtained by the Embletta and PSG. The Embletta device does not record sleep, and sleep onset and awakening times are inferred from a combination of breathing pattern, movement and information provided by the patient. As a result, events occurring whilst the patient is awake may be included in the A+H per hour in bed. This therefore differs fundamentally from the AHI calculated from PSG. The favourable results of the synchronous study do not indicate a sensor problem with the Embletta as the cause, although it is interesting to note the difference in oximetry results between the two systems.

Significant night-to-night variation in respiratory events has been demonstrated in OSAHS and, indeed, is more marked in those with mild OSAHS.(198) Patients may sleep better in the home environment compared to the unfamiliar surroundings of the sleep laboratory. Body position, with more time spent supine in-laboratory than at

home, is another extremely important factor which may contribute to the observed differences.(199) Indeed we have also shown that time spent supine and A+H were greater in-laboratory compared to at home. It may be therefore that the home, rather than in-laboratory, study is a more accurate reflection of the 'true' burden of SDB.

These technical and situational factors may be further influenced by the differing characteristics of the patient population being studied. Differences between apnoea/hypopnoea measures observed in the current study were approximately twice those of comparable studies in patients with suspected OSAHS from the general population.(22;115;116) These studies all showed a tendency for the portable study to underestimate the PSG AHI. One possible reason to account for this greater difference is the reduced total sleep time and poorer sleep efficiency amongst patients with CHF.(22;23) Mean sleep efficiency recorded in this study was  $57 \pm 21$  %, compared to  $76 \pm 2$  % in a similar study conducted by our group in sleepy patients with suspected OSAHS.(114) As a result, sleep, and its associated respiratory events, occurs for a smaller proportion of the night leading to greater underestimation of event rate by the Embletta. Many factors may contribute to poor sleep efficiency in CHF patients. These include both symptoms of CHF, such as orthopnoea, paroxysmal nocturnal dyspnoea and nocturia, and other factors, such as more advanced age and associated co-morbidity, unwanted effects of medication and psychosocial effects of chronic illness. These symptoms of CHF may also fluctuate further contributing to variation in respiratory event rates. Also, CHF patients are generally less active than OSAHS patients, and subjectively less sleepy.

Our results contrast with previous work comparing a different home limited sleep study (Apnoescreen II; Erich Jaeger GmbH & CoKG, Wuerzburg, Germany), which used thermistors to detect airflow, with PSG on separate nights for the diagnosis of SDB in CHF.(197) This group reported high sensitivity and specificity, indeed achieving higher values than in studies for the diagnosis of OSA in patients without CHF, which is perhaps surprising when the factors discussed above are taken into consideration. Others have reported promising results with overnight home oximetry as a tool for identifying SBD in patients with CHF, but this technique is limited by the inability to distinguish between obstructive and central events.(200;201)

The study patient group was recruited from our local CHF out-patient cardiology clinic population. The total percentage of patients found to have SDB (58%), based on PSG  $AHI \geq 15$ , was comparable with previous studies of CHF and SDB.(23;49) However, in contrast to earlier studies which have reported a prevalence of CSA in CHF patients of up to 45%,(23;49;52) we found predominant CSA in only one of our twenty patients and a very low central apnoea index across the group as a whole. This may be explained by our modest sample size but may also be due to differences in scoring techniques and classification criteria between sleep laboratories, in addition to advances in pharmacological therapy.

### **3.5.1 Study Limitations**

Limitations of this study include the site of the studies and the sample size. We performed the synchronous study in the sleep laboratory setting since this is the location where most diagnostic studies are performed and because in-laboratory PSG is the

nearest to a gold standard that exists. We did not perform synchronous PSG during the home studies as it was our aim to evaluate the Embletta as it would be used in the clinical setting. However, we cannot therefore prove whether sleep quality was also poorer in the home setting for these CHF patients. Furthermore, we did not assess night-to-night variability in this study, which may have contributed to our findings. We believe that the sample size was adequate to demonstrate good agreement between the Embletta and PSG in the synchronous study and also to provide important insight into the potential use and limitations of the Embletta device as a diagnostic tool in the home environment. However, we accept that the modest sample size may have contributed to our findings of poor agreement between home Embletta and PSG. Based on our previous work in patients with OSAHS, the study had 80% power to detect a difference of 8 in A+H between home Embletta and PSG.(114)

Another theoretical limitation might be differences in technology used by the two devices. The Embletta, for example, used a different oximeter to the PSG. However, as we used the American Academy of Sleep Medicine definition of significant respiratory events, which does not require desaturation, this would not affect the results.(202) Some of the published studies did require desaturation for a significant event to occur and thus their identification of events would both be oximeter dependent and vary with the extent of hypoxaemia of the patient, and thus reflect severity of CHF, age and lung disease. Also of note, the Embletta studies did not include ECG monitoring and therefore do not provide information regarding heart rate, rhythm and ECG morphology, changes in which may be frequent in this population.

Both systems recorded flow by nasal pressure as well as thoraco-abdominal movement and used these signals to define hypopnoeas. Hypopnoeas cannot be differentiated with certainty between central or obstructive from surface techniques and therefore we report events/hr rather than central events and obstructive events separately.

### **3.5.2 Conclusions**

Agreement in diagnostic outcome between home limited sleep studies and in-laboratory PSG, and the negative predictive value of the home limited sleep study, were poor. These findings may be explained by both technical and situational factors which may be more marked in this patient population with poor sleep efficiency, and should be taken into consideration when considering potential screening or diagnostic tools for sleep-disordered breathing in patients with CHF.



## **CHAPTER 4**

### **SLEEP DISORDERED BREATHING IN PATIENTS WITH CHRONIC HEART FAILURE**

*Contemporary prevalence and characteristics*

Smith LA, Vennelle M, Denvir MA, Douglas NJ, Newby DE. Contemporary prevalence and characteristics of sleep-disordered breathing in patients with chronic heart failure.

Submitted.

## 4.1 SUMMARY

The aim of this study was to evaluate prospectively the prevalence and type of SDB in patients with CHF receiving contemporary modern therapy. Eighty-five patients with stable symptomatic CHF underwent screening for SDB by home sleep study. Daytime sleepiness was assessed by the Epworth Sleepiness Scale and CHF severity by symptom class, LVEF and serum NT-proBNP. Patients ( $61\pm 9$  years, LVEF  $28\pm 9\%$ ) were treated with ACE inhibition or angiotensin receptor blockade (95%), beta-blockade (76%), spironolactone (38%), diuretics (82%) and digoxin (32%). SDB [ $\geq 15$  apnoeas/hypopnoeas (A+H) per hour] was present in 23 (27%) patients (A+H  $25\pm 9/h$ , oxygen desaturations  $20\pm 13/h$ ). Of these, 22 patients (26%, 95% confidence interval 17-36%) had obstructive sleep apnoea (OSA) and only one had central sleep apnoea (1%, 95% confidence interval 0-7%). There were no differences in symptom class, LVEF, NT-proBNP or Epworth Sleepiness Score between those with and without SDB. There was no correlation between A+H and LVEF ( $r_s = -0.02$ ,  $p = 0.87$ ) or NT-proBNP ( $r_s = 0.23$ ,  $p = 0.06$ ). SDB is common in patients with stable CHF but is difficult to diagnose because of the major overlap in symptomatology. In the era of modern therapy, SDB is predominantly OSA with no clear relationship with severity of CHF.

## 4.2 INTRODUCTION

SDB is characterised by recurrent apnoeas and hypopnoeas with disruption of normal ventilation and sleep architecture. The prevalence of SDB in the healthy middle-aged population is estimated to be 4-9%.(34) In contrast, early studies have reported that SDB is very common in ambulatory patients with CHF: up to 62% depending on diagnostic threshold and selection criteria chosen.(23;49;52) However, these data predate recent important advances in drug and device therapy, which have improved morbidity and mortality,(15-17) and are now widely adopted in guidelines for the optimal management of patients with CHF.(1;7)

SDB in patients with CHF often passes unrecognized and yet is associated with increased morbidity and mortality and presents a potential therapeutic target.(51;107) SDB is associated with systemic hypertension,(76;80) increased inflammatory mediator concentrations,(81) increased sympathetic nervous system activation,(93) vascular endothelial dysfunction(78) and adverse cardiac performance:(79) all mechanisms by which SDB may contribute to the progression of CHF. Most studies have reported a predominance of CSA rather than OSA.(23;49;52) However, CSA is associated with markers of increased severity of CHF(55-58) and its presence may be simply an indicator of decompensated heart failure and elevated left ventricular filling pressures. Indeed, patients receiving interventions of proven benefit in CHF, namely beta-blocker and cardiac resynchronization therapy, have a lower prevalence and severity of CSA.(110;111)

The aims of the study were to determine prospectively the prevalence of SDB in patients with stable symptomatic CHF on optimal medical therapy according to contemporary guidelines and also to investigate the clinical characteristics of patients with SDB compared to those without SDB. We hypothesised that the prevalence of SDB would be lower than previously reported and that this would be due mainly to reduction in CSA.

## **4.3 METHODS**

### **4.3.1 Participants**

Patients were recruited from general cardiology clinics at two university hospitals in Edinburgh and from a specialist heart failure clinic in Glasgow. Consecutive patients aged between 18 and 80 years with symptomatic (NYHA class II-IV) but stable CHF for at least one month on maximally tolerated medical therapy and objective evidence of left ventricular systolic dysfunction (echocardiographic LVEF < 45%) were enrolled into this prospective study. Exclusion criteria were acute coronary syndrome within the preceding three months, implantation of a pacemaker or defibrillator within the preceding six months, primary valvular heart disease, sustained ventricular arrhythmias (but not atrial fibrillation) and stroke with residual neurological deficit. The study conformed to the principles outlined in the Declaration of Helsinki, the protocol had the approval of the local ethics committees and all patients provided written informed consent.

### **4.3.2 Procedures**

#### **4.3.2.1 Study protocol**

Study participants underwent detailed clinical assessment, symptomatic evaluation (NYHA class and ESS), transthoracic echocardiography, blood sample collection and home limited sleep study. Investigations were performed within a 4 week period with clinical stability in all patients.

#### 4.3.2.2 Sleep study recordings

Limited sleep studies were performed using a commercially available system (Embletta; Flaga, Iceland) measuring: 1) nasal pressure using a nasal cannula/pressure transducer system (recording the square root of pressure as an index of flow), 2) thoraco-abdominal movement from two piezoelectric belts, 3) finger pulse oximetry and 4) body position. Patients were educated in the application of the Embletta device prior to the study and applied the device themselves at home. They were provided with written instructions and a night-time telephone number to call in the event of difficulties. Patients required sufficient agility to apply the thoraco-abdominal bands, nasal cannula and pulse oximeter and connect a single connector to the recording device. No calibration was required.

#### 4.3.2.3 Sleep study analysis

All sleep studies were scored according to standard criteria by the same experienced sleep technician (M.V.) who was blinded to the patients' identities.(177) Apnoeas were defined as a complete cessation in airflow lasting  $\geq 10$  s, and hypopnoeas as a reduction in airflow or thoraco-abdominal movement by  $\geq 50\%$  for  $\geq 10$  s. Apnoeas were classified as 1) *obstructive* if thoraco-abdominal movement was present during the apnoea; 2) *central* if thoraco-abdominal movement was absent; and 3) *mixed* if thoraco-abdominal movements were both present and absent during the period of airflow cessation.(30) Analysis was started once respiration settled to a stable rhythmic pattern and stopped either according to the time of awakening as provided by the patient or based on tracing quality and breathing pattern.

#### **4.3.2.4 Echocardiography**

Trans-thoracic Doppler echocardiography was performed by a single, experienced and blinded research sonographer using an ATL HDI 5000 system (Philips Medical Systems Limited, Stevenage, U.K). Left ventricular volumes and ejection fraction were calculated according to modified Simpson's rule.

#### **4.3.2.5 Neurohumoral markers**

Blood samples were collected in EDTA with additive trasylol and spun at 1000 *g* for 20 minutes at 4<sup>0</sup>C. The plasma was then extracted and frozen in aliquots at -40 <sup>0</sup>C until analysis. N-terminal pro-brain natriuretic peptide (NT-proBNP) concentrations were measured using a chemiluminescent immunoassay (Roche Diagnostics Ltd, Lewes, U.K.) on an Elecsys 2010 analyser.

#### **4.3.3 Statistical analysis**

Statistical analyses were performed using Statistical Package for Social Sciences version 10 software (SPSS inc., Chicago, U.S.A). Continuous variables are expressed as mean values ( $\pm$ SD), or when not normally distributed data as medians (interquartile range). Differences between groups were assessed by two-tailed, unpaired t-tests. NT-proBNP data were normalised by logarithmic transformation prior to analysis.

## **4.4 RESULTS**

### **4.4.1 Patient Characteristics**

Eighty-five patients with stable symptomatic CHF were screened for SDB by home limited sleep study (Table 4.1). Patients were predominantly male (87%) with a mean age of  $61 \pm 9$  years, overweight [BMI  $30 \pm 5$  kg/m<sup>2</sup>] and had moderately severe CHF (LVEF  $28 \pm 9\%$ ) of predominantly ischaemic aetiology. They were predominantly NYHA class 2 and only 18 (21%) reported excessive daytime sleepiness (ESS>10). Patients were on appropriate contemporary medical therapy for CHF due to left ventricular systolic impairment, including ACE inhibition or angiotensin II receptor blockade in 95%, beta-blockade in 76% and spironolactone in 38%.

### **4.4.2 Prevalence and type of sleep-disordered breathing**

Significant SDB [ $\geq 15$  apnoeas/hypopnoeas (A+H) per hour in bed] was present in 23 (27%) patients (A+H  $25 \pm 9$  /h) and they had an increased frequency in oxygen desaturation ( $20 \pm 13$  /h v  $7 \pm 5$  /h,  $p < 0.001$ ) (Table 4.2). Of these, 22 (26% total) had predominant OSA and only 1 (1% total) predominant CSA. Using a lower threshold of  $A+H \geq 10$  /h, the prevalence of SDB increased to 42%, but only 1 further patient was identified with predominant CSA. Seven (8%) patients had  $A+H \geq 30$  respiratory events per hour.

### **4.4.3 Characteristics of patients with sleep-disordered breathing**

Patients with SDB were more likely to have hypertension (57% v 27%,  $p = 0.02$ ) but there were no differences in age, sex, body mass index, aetiology of CHF or the



presence of diabetes or atrial fibrillation between the two groups (Table 4.1). The prevalence of SDB did not differ when patients were stratified according to BMI (BMI  $\geq 30$  kg/m<sup>2</sup>, 28%; BMI  $< 30$  kg/m<sup>2</sup>, 30%,  $p=0.81$ ). Patients with and without SDB did not differ in terms of severity of CHF (NYHA class, LVEF, NT-proBNP) or in subjective assessment of symptoms (NYHA class, ESS) (Table 4.2). Furthermore, there was no correlation between A+H and LVEF ( $r_s=-0.02$ ,  $p=0.87$ ) and only an apparent trend towards a correlation between A+H and NT-proBNP ( $r_s=0.23$ ,  $p=0.06$ ) (Figures 4.1 and 4.2). ESS did not correlate with A+H ( $r_s=0.05$ ,  $p=0.64$ ). The only univariate predictor of SDB identified in this group of patients with CHF was hypertension [odds ratio 3.44 (1.27-9.31),  $p=0.02$ ].

**Table 4.1**

	<b>All (n=85)</b>	<b>No SDB (n=62)</b>	<b>SDB (n=23)</b>	<b>P value</b>
Age (years)	61±9	60±10	63±8	0.11
Sex (male:female)	74:11	52:10	22:1	0.27
Body mass index (kg/m <sup>2</sup> )	30±5	30±5	30±5	0.51
CHF aetiology (ischaemic:non)	54:31	37:25	17:6	0.31
Hypertension	30 (35%)	17 (27%)	13 (57%)	0.02
Diabetes mellitus	15 (18%)	9 (15%)	6 (26%)	0.22
Atrial fibrillation	21 (25%)	14 (23%)	7 (30%)	0.57
Drug treatment				
ACEI / ARB	81 (96%)	60 (97%)	21 (91%)	0.29
Beta blockade	67 (79%)	52 (84%)	15 (65%)	0.17
Digoxin	30 (37%)	20 (32%)	10 (43%)	0.44
Diuretics	70 (83%)	51 (82%)	19 (83%)	1.00
Spironolactone	32 (38%)	23 (37%)	9 (39%)	1.00
NYHA class	2.2±0.5	2.2±0.4	2.3±0.6	0.22
Never smoked	26 (31%)	18 (29%)	8 (35%)	0.79

ACEI: angiotensin converting enzyme inhibition, ARB: angiotensin receptor blockade, NYHA: New York Heart Association.

**Table 4.2**

	No SDB (n=62)	SDB (n=23)	P value
<b>Sleep Data (per hour)</b>			
A+H	7±4	25±9	<0.001
Obstructive apnoeas	1±1	6±5	<0.001
Central apnoeas	0±1	3±5	<0.001
Mixed apnoeas	0±0	0±1	0.048
Hypopnoeas	6±3	16±6	<0.001
O <sub>2</sub> desaturations ≥4%	7±5	20±13	<0.001
<b>Echocardiography</b>			
LA diameter (mm)	44±7	47±9	0.26
LVEDD (mm)	60±12	65±10	0.06
LVESD (mm)	50±11	52±9	0.40
Fractional shortening (%)	19±7	18±6	0.60
LVEF (%)	29±9	27±7	0.41
<b>Neurohumoral markers</b>			
NT-proBNP (pg/mL)	810 (1623)	1693 (2430)	0.18
<b>Symptoms</b>			
NYHA class	2.2±0.4	2.3±0.6	0.22
ESS	7±4	7±4	0.84

A+H: apnoeas + hypopnoeas, LVEDD: left ventricular end-diastolic dimension, LVESD: left ventricular end-systolic dimension, LVEF: left ventricular ejection fraction, NT-proBNP: N-terminal pro-brain natriuretic peptide, NYHA: New York Heart Association, ESS: Epworth Sleepiness Score

Figure 4.1

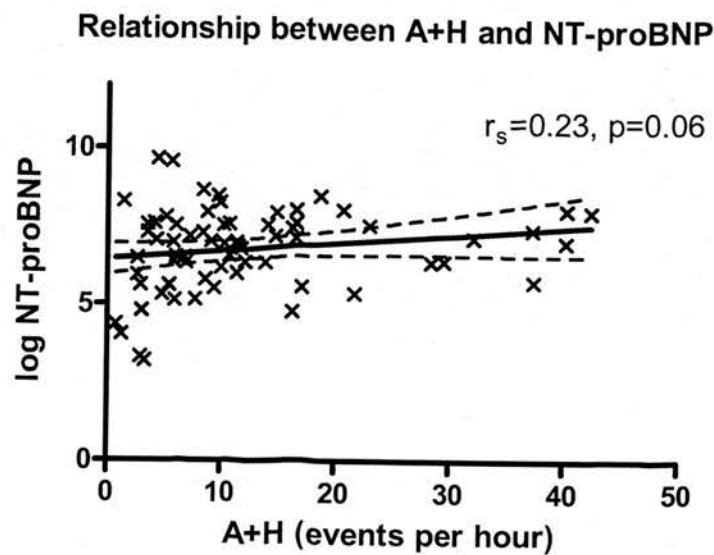
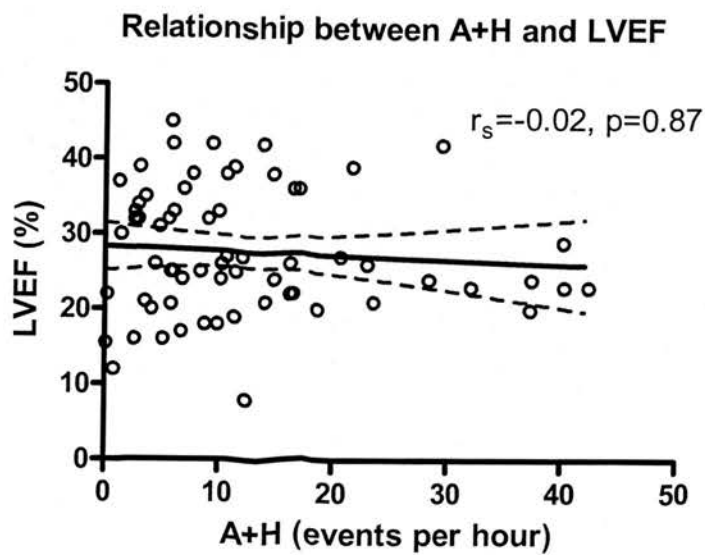


Figure 4.2



## 4.5 DISCUSSION

SDB remains common in patients with symptomatic stable CHF but is difficult to diagnose because of the major overlap in symptomatology. However, in the era of modern CHF therapies, SDB is predominantly OSA and CSA is now relatively unusual. Furthermore, there is no clear relationship with the severity of CHF, and characteristics such as increased BMI and subjective daytime sleepiness are much less helpful in this patient population than in OSAHS.

### 4.5.1 Changing prevalence & type of sleep-disordered breathing

Our data show the prevalence of significant SDB, defined by  $A+H \geq 15$  events per hour, was 27% in this cohort of patients with stable symptomatic CHF, with a predominance of OSA (26%) compared to CSA (1%). This lower prevalence of SDB is approximately half the reported rate and is attributable to a marked reduction in CSA, with earlier studies reporting a prevalence of CSA varying between 29 and 62% in patients with CHF.(23;49;51;52;107;203) In comparison to these previous studies, our patients were similar in terms of age, sex and NYHA class although LVEF (28% v 21-23%) and BMI (30 kg/m<sup>2</sup> v 26-28 kg/m<sup>2</sup>) were slightly higher. It should be noted that the patients studied retrospectively by Sin *et al* were a selected group in that they had been referred to a sleep laboratory with clinical suspicion of SDB.(23) There were differences in the type of sleep studies, scoring criteria and diagnostic thresholds employed. However, even adopting the lower threshold for SDB used by Lanfranchi *et al*, prevalence in this study is still only 42% compared to 74%.(51) We suggest that this lower prevalence of SDB, with the observed reduction in CSA, is due to improvements in the modern

treatment of patients with CHF. Previous studies largely predate the routine use of beta-blockade, spironolactone and angiotensin II receptor blockade in this patient population and the percentage of patients receiving ACE inhibition was lower.(23;49;51;52;107;203)

More recent data are conflicting with an overall prevalence of SDB of between 24 and 71% with no consensus on the predominant type of SDB.(55-60) In keeping with our findings, others have reported a reduction in CSA.(55;60;109) There is undoubtedly some variation in patient characteristics between studies, and indeed CSA is known to be associated with severely reduced LVEF and higher NYHA class. However, patients were generally maintained on current optimal medical therapy, and the discrepancy in findings from studies examining the prevalence and type of SDB in the stable out-patient CHF population may largely be explained by the differing types of sleep study, scoring criteria and diagnostic thresholds. This lack of standardisation makes comparison difficult.

Classification of respiratory events into obstructive or central may be challenging and both often coexist in the same patient. Currently there is clinical uncertainty and no uniform consensus regarding the definition of a hypopnoea.(112) Groups differ in whether oxygen desaturation (of varying magnitude) and/or arousal are required for a hypopnoea to be identified and this is further influenced by the type of equipment utilised to detect changes in breathing. Identification of events is therefore both oximeter dependent and varies with the extent of hypoxaemia, thus reflecting severity of CHF, age and lung disease. A number of differing technologies to determine respiratory

effort are available increasing variability in results. Pneumotachography and body plethysmography have traditionally been considered the gold standards for assessment of tidal volume and or flow rate, and thus detection of apnoeas and hypopnoeas. Pharyngeal and oesophageal manometry can be used to determine estimates of airflow and respiratory effort. However, none of these techniques is suitable for routine PSG. Thermal and nasal pressure sensors, and inductance plethysmography, are therefore widely used in sleep laboratories as physiological sensors, but have some limitations. Thermal sensors, in particular, do not provide quantitative measures of airflow for detection of hypopnoeas.(204;205) Nasal pressure transducers, adapted to detect flow limitation, improve hypopnoea detection and have been validated against pneumotachography, as has calibrated inductance plethysmography, although the systems used are generally uncalibrated.(204;206;207) Pulse transit time may be used as a surrogate marker of oesophageal pressure to aid detection and classification of events.(208;209) Supplementary information gained from the sleep study, such as interrogation of the snoring channel, may also aid the scorer. However, it is clear that differences in both techniques and technologies utilised to perform the sleep study, and in its scoring and interpretation, will affect intra and interlaboratory variability and published data.

The distinction between OSA and CSA is clinically relevant because it influences treatment strategy. Randomised controlled trials in patients with OSA and CHF have shown that CPAP improves quality of life, reduces blood pressure and sympathetic nervous system activity, and may improve cardiac function.(142;144;210) The management of CSA however, other than by optimisation of CHF therapy, is more

controversial. CPAP and adaptive servo-ventilation improve daytime sleepiness, cardiac function and sympathetic activity but the recently reported CANPAP trial did not demonstrate a beneficial effect of CPAP on morbidity or mortality in patients with CHF and CSA. (106;109;147;158;163)

#### **4.5.2 Characteristics of patients with chronic heart failure and sleep-disordered breathing**

It would be extremely useful to be able to predict which patients with CHF have a higher likelihood of SDB and would therefore benefit from sleep assessment and, in the setting of symptomatic OSA, CPAP or non-invasive ventilation. This is particularly important given the often slow access to sleep studies.(113)

Whilst we have shown that SDB (essentially OSA) remained relatively common in this population, its presence did not impact on symptoms, functional status or measures of severity of CHF. Patients with SDB were more likely to have hypertension than those without SDB, an interesting observation in this cohort of patients with CHF due to impaired LV systolic function. In patients with normal LV systolic function, the results of large epidemiological studies support a causative role for OSA in the development of systemic hypertension, independent of other potential confounding variables.(33;80;211-213) Furthermore, treatment of OSA with CPAP has been shown to lower both daytime and nocturnal blood pressure.(76;124;125) Control of blood pressure is extremely important in patients with CHF, and the development or exacerbation of systemic hypertension associated with OSA presents one potential mechanism by which the progression of CHF may be accelerated.



There were no differences in age, gender, BMI, aetiology of CHF, drug therapy or the presence of diabetes or atrial fibrillation between those patients with SDB and those without SDB. The ESS was not a helpful tool in predicting SDB, as reported elsewhere.(59;195) This is perhaps unsurprising as there is considerable overlap between the symptoms of CHF and SDB, and although these patients have objectively measured daytime sleepiness, few actually complain of it.(22;49;195) Sin *et al* found BMI  $>35 \text{ kg/m}^2$  to be a risk factor for OSA in men with CHF (odds ratio 6.10[2.86-13.00]) but in our patient cohort, and others, this was not a helpful discriminator.(23;55;57)

Central sleep apnoea was rare in our study population and therefore our findings do not enable us to examine the characteristics of patients with heart failure and CSA. Previously identified risk factors for CSA include age  $> 60$  years, male gender, atrial fibrillation and hypocapnia; others report an association between CSA and indices of increased severity of CHF.(23;55-58) However, it is difficult to know whether these indices are simply a reflection of more severe CHF rather than the presence of CSA. Furthermore, comparisons in the literature between groups of CHF patients with OSA and CSA need to be interpreted with care as there are often significant differences in apnoea/hypopnoea index (AHI) and CHF indices between groups.

#### **4.5.3 Study limitations**

We used a limited sleep study to evaluate SDB rather than in-laboratory PSG, which many regard as the gold standard. Limited studies are a more accessible alternative to

full PSG and have been well validated against PSG in the investigation of OSAHS in the general population.(113;114;119) Patients may not sleep as well in the unfamiliar surroundings of the sleep laboratory and it may be that a home study is a more accurate reflection of the true burden of SDB. However, there is a tendency for limited studies, which record respiratory events per hour in bed rather than per hour of sleep, to underestimate the PSG AHI.(22;115;116) This may be exaggerated further by the reduced total sleep time and poorer sleep efficiency observed in patients with CHF.(22;23) It is possible that, in comparison to studies conducted using PSG, the prevalence of SDB has been underestimated in our study and, as such, does not reflect the true prevalence of SDB in the CHF population. However, previous studies using similar techniques still found a high prevalence of SDB and CSA.(51;57;60) It is also not possible to assess the presence of periodic limb movements during sleep with our limited studies and this disorder itself may impact on symptoms.

Whilst some groups attempt to classify hypopnoeas, we believe these cannot be differentiated definitively with surface techniques, and therefore have not attempted to do so. However, we acknowledge that, particularly where hypopnoeas rather than apnoeas predominate, this may influence the designated type of SDB. This is one reason which may help explain the low prevalence of CSA in our study, in addition to the differences in prevalence of SDB reported in the literature.

Patients with recent implantation of a cardiac pacemaker or defibrillator were excluded from this study. As cardiac resynchronization therapy becomes more widespread this may perhaps further reduce the prevalence of SDB.

Finally, participants in CHF research studies tend to be younger, well-motivated and have fewer comorbidities than non-participants and thus our cohort of patients may not be characteristic of the wider CHF population.(214;215)

#### **4.5.4 Conclusions**

Sleep-disordered breathing remains relatively common in patients with stable CHF on optimal contemporary medical therapy. However, contrary to previous data, this is predominantly OSA and CSA is now rare. It is difficult to identify SDB clinically in patients with CHF: ESS score and BMI are less helpful in this patient population. Clinicians should be alert to the presence of, and the requirement for sleep studies to diagnose SDB in patients with CHF. Furthermore, there is a need for greater standardisation in scoring and classification criteria for SDB in CHF to enable meaningful comparisons and appropriate treatment decisions to be made.

## CHAPTER 5

# **AUTO-TITRATING CONTINUOUS POSITIVE AIRWAY PRESSURE THERAPY IN PATIENTS WITH CHRONIC HEART FAILURE AND OBSTRUCTIVE SLEEP APNOEA *A RANDOMISED PLACEBO CONTROLLED TRIAL***

Smith LA, Vennelle M, Gardner RS, McDonagh TA, Denvir MA, Douglas NJ, Newby DE. Auto-titrating continuous positive airway pressure therapy in patients with chronic heart failure and obstructive sleep apnea: A randomized placebo controlled trial.  
*Eur Heart J* 2007;28:1221-1227

## 5.1 SUMMARY

Obstructive sleep apnoea is highly prevalent in patients with CHF and may contribute to CHF progression. We aimed to determine whether treatment of OSA with CPAP would improve subjective and objective measures of heart failure severity in patients with CHF and OSA. 26 patients with stable symptomatic CHF and OSA were randomised to nocturnal auto-titrating CPAP or sham CPAP for 6 weeks each in crossover design. Study co-primary endpoints were changes in peak  $\text{VO}_2$  and 6-minute walk distance. Secondary endpoints were changes in LVEF,  $\text{VE}/\text{VCO}_2$  slope, plasma neurohormonal markers and quality of life measures. 23 patients completed the study protocol. Mean CPAP and sham CPAP usage were  $3.5 \pm 2.5$  and  $3.3 \pm 2.2$  h/night respectively ( $p=0.31$ ). CPAP treatment was associated with improvements in daytime sleepiness (ESS score  $7 \pm 4$  vs  $8 \pm 5$ ,  $p=0.04$ ) but not in other quality of life measures. There were no changes in other study endpoints. In patients with CHF and OSA, auto-titrating CPAP improves daytime sleepiness but not other subjective or objective measures of CHF severity. These data suggest that the potential therapeutic benefits of CPAP in CHF are achieved by alleviation of OSA rather than by improvement in cardiac function.

## 5.2 INTRODUCTION

Chronic heart failure is a major cause of morbidity and mortality in developed countries and its prevalence and incidence continues to rise.(3) The Sleep Heart Health Study has shown a cross-sectional association between OSA and CHF.(98) Although often unrecognised, OSA is highly prevalent in patients with CHF: up to 37%, depending on diagnostic threshold and selection criteria chosen.(23;49) Furthermore, severe OSA is an independent risk factor for fatal and non-fatal cardiovascular events, and this risk may be reduced by the application of nocturnal CPAP.(97)

Obstructive sleep apnoea is characterised by intermittent partial or complete upper airway obstruction during sleep disrupting normal ventilation and sleep architecture. OSA is associated with systemic hypertension,(76;80;216) vascular endothelial dysfunction,(77;78) increased sympathetic nervous activity(82) and increased levels of inflammatory mediators.(81) In addition, inspiration against the occluded upper airway generates exaggerated negative intra-thoracic pressure which adversely affects cardiac performance.(74) These important factors are all implicated in the development and progression of CHF.

There have been only two previous randomised controlled trials to assess CPAP in patients with CHF and OSA.(142;144) These trials report improvements in left ventricular ejection fraction, overnight urinary norepinephrine excretion, systolic blood pressure and some quality of life measures. However, they employed parallel group

comparisons with small numbers of patients ( $n=12-19$  *per* group) and, importantly, no appropriate placebo control.

The aim of this study therefore was to determine whether, using a double blind randomised placebo controlled crossover trial, treatment of OSA by nocturnal auto-titrating CPAP would improve subjective and objective measures of CHF severity.

## **5.3 METHODS**

### **5.3.1 Participants**

Patients were recruited from general cardiology clinics at two university hospitals in Edinburgh and from a specialist heart failure clinic in Glasgow. Consecutive patients with CHF aged between 18 and 80 years were enrolled into this prospective study if the following inclusion criteria were met: 1) symptomatic CHF (NYHA class II-IV), 2) LVEF determined by echocardiography of  $< 45\%$ , 3) clinical stability for at least one month, 3) optimal medical therapy, and 4)  $AHI \geq 15$  (predominantly obstructive) on PSG. Exclusion criteria were acute coronary syndrome within the preceding three months, primary valvular heart disease, sustained ventricular arrhythmias (but not atrial fibrillation) and stroke with residual neurological deficit. The study complied with the Declaration of Helsinki, the protocol had the approval of the local ethics committee and all patients provided informed written consent.

### **5.3.2 Procedures**

#### **5.3.2.1 Sleep studies**

Patients with 15 or more apnoeas/hypopnoeas per hour in bed on a limited sleep study performed at home were invited to attend for PSG at the Sleep Centre in Edinburgh. PSG was performed following our standard laboratory protocol (172) with a computerised recording system (Compumedics, Abbotsford, Australia) consisting of: 1) sleep monitoring through electro-encephalogram, electro-oculogram, and submental plus outer canthi electromyogram, 2) bilateral tibial electromyogram and body position



detector, 3) nasal pressure using a nasal cannula/pressure transducer system, 4) thoraco-abdominal movement from two inductance plethysmographic belts, 5) finger pulse oximetry, 6) snoring detection by digital microphone and 7) three-lead electrocardiogram.

All sleep studies were scored according to standard criteria by the same experienced sleep technician.(177) Apnoeas were defined as a complete cessation in airflow lasting  $\geq 10$  s, and hypopnoeas as a reduction in airflow or thoraco-abdominal movement by  $\geq 50\%$  for  $\geq 10$  s. Apnoeas were classified as 1) *obstructive* if thoraco-abdominal movement was present during the apnoea; 2) *central* if thoraco-abdominal movement was absent; and 3) *mixed* if thoraco-abdominal movements were both present and absent during the period of airflow cessation. (30)

### 5.3.2.2 Study protocol

This was a double-blind randomised placebo controlled crossover trial in patients with CHF and OSA. Patients were randomised to nocturnal auto-titrating CPAP (Autoset Spirit: ResMed, Sydney, Australia) and sham CPAP for 6 weeks each in a cross-over design with a 1 week washout period. Randomisation to treatment order was performed following baseline assessment using sealed envelopes and a balanced block design with 6 patients per block. Study co-primary endpoints were changes in peak  $\text{VO}_2$  and 6-minute walk distance. Secondary endpoints were changes in LVEF,  $\text{VE}/\text{VCO}_2$  slope, plasma neurohormonal markers and quality of life measures.

Auto-titrating CPAP automatically adjusts pressure according to upper airway obstruction, avoiding many of the disadvantages of titration and treatment with

conventional CPAP. It is as effective as fixed pressure CPAP in reducing daytime sleepiness and AHI, and also increases nightly use, provides better quality sleep and less discomfort.(133;134) Sham CPAP was chosen as the placebo in the present study because it was felt important to control for the discomfort and possible sleep disruption of wearing a mask overnight; it also makes observer blinding easier to maintain. The sham device was created by setting delivered airway pressure to a minimum, insertion of a flow restricting connector at the machine outlet and creation of an extra hole in the collar of the main tubing at the end of the mask.(180) . The device delivered a CPAP pressure of approximately 1 cm H<sub>2</sub>O.

Patients underwent an initial daytime education session and were then supervised for their first night on each device in the Sleep Centre. They were asked to use the machine for a minimum of six hours per night at home and provided with a contact telephone number in case of any problems. In addition, all patients were contacted by telephone by the Sleep Centre Research Nurse within 2 weeks of taking each device home. Compliance with therapy was assessed by interrogation of the CPAP unit to provide nightly usage data.

Study investigators performing assessments were blinded to treatment modality; they were not involved in randomisation, device education or follow-up and study participants were instructed not to discuss their device with them. Study participants themselves were advised that two different types of breathing device were being tested and that they would receive both in a random order.

Functional evaluation was performed at the coordinating centre at baseline, 6 and 13 weeks and included: 1) clinical assessment, 2) trans-thoracic echocardiography, 3) symptom-limited cardiopulmonary exercise testing, 4) 6 minute walk test, 5) neurohumoral markers, 6) OSLER test (175) and 7) quality-of-life assessment. At baseline evaluation, two 6 minute walk and two cardiopulmonary exercise tests were performed on separate days to minimise any potential bias due to a training effect; the second tests were taken as baseline data.

#### **5.3.2.3 Cardiopulmonary exercise testing**

Symptom-limited exercise tests were performed under physician supervision using an electronically-braked cycle ergometer. The incremental exercise protocol was individualised aiming for exercise duration between 8 and 12 minutes.(190) A 12-lead electrocardiogram was monitored continuously during the test and cuff blood pressure was recorded manually every two minutes. Patients were asked to exercise to exhaustion and all tests were conducted under physician supervision. Respiratory gas exchange measurements were obtained breath-by-breath using a computerised metabolic cart (MSX, Ferraris Group Plc, Birmingham, U.K). Gas and flow calibrations were performed before each test.

Breath-by-breath data were formatted using a rolling eight breath average. Peak  $\text{VO}_2$ ,  $\text{VCO}_2$  and  $\text{VE}$  were recorded as the highest such values within the last 30 seconds of the test. Predicted peak  $\text{VO}_2$  values were calculated using the standard formulae described by Wasserman *et al.*(191) The anaerobic threshold was determined non-invasively using a dual method (V-slope and ventilatory equivalents) approach as the respiratory

exchange ratio approximated unity.(192) The  $VE/VCO_2$  slope was calculated as a linear regression function, excluding the non-linear part of the relationship after the onset of acidotic drive to ventilation.(190)

#### **5.3.2.4 Six minute walk test**

A standardised test procedure was followed.(189) Patients were asked to walk around a walking track, covering as much distance as possible during 6 minutes, and were allowed to rest if required.

#### **5.3.2.5 Echocardiography**

Trans-thoracic Doppler echocardiography was performed by a single, experienced research sonographer using an ATL HDI 5000 system (Philips Medical Systems Limited, Stevenage, U.K). Left ventricular volumes and ejection fraction were calculated according to modified Simpson's rule.

#### **5.3.2.6 Clinical and Quality-of-Life Assessment**

Clinical assessment was performed at each study visit and NYHA class recorded. Standardised questionnaires (SF-36, Minnesota Living with Heart Failure and Epworth Sleepiness Scale (188)) were used to assess quality of life and symptoms.

#### **5.3.2.7 Neurohumoral markers**

Blood samples were collected in EDTA with additive trasylol or 2% sodium metabisulphite and spun at 1000 g for 20 minutes at 4°C. The plasma was then extracted and frozen in aliquots at -40 °C until analysis. NT-proBNP and NT-proANP were

measured using a chemiluminescent immunoassay (Roche Diagnostics Ltd, Lewes, U.K.) on an Elecsys 2010 analyser. Plasma norepinephrine concentrations were determined by an electrochemical method after separation by reverse phase high performance liquid chromatography.(193)

### **5.3.3 Statistical analysis**

Statistical analyses were performed using Statistical Package for Social Sciences version 10 software (SPSS inc., Chicago, U.S.A). Continuous variables are expressed as mean values ( $\pm$ SD), or when not normally distributed data as medians (interquartile range). Differences between the changes in outcome measures with intervention, *i.e.* CPAP and sham CPAP, were compared by two-tailed, paired t-tests. NT-proBNP and NT-proANP data were normalised by logarithmic transformation prior to assessment. The study had 80% power, at 5% significance level, to detect absolute differences in the primary end-points of 1.1 mL/min/kg in peak  $\text{VO}_2$  and 33 m in 6-minute walk distance, assuming standard deviation of expected changes of 1.9 mL/min/kg and 57 m respectively. Statistical significance was taken at the 5% level.

## 5.4 RESULTS

Of the 349 patients who potentially fulfilled the entry criteria, 114 consented to undergo study screening (Figure 5.1). Sleep studies were performed on 103, with 46 subsequently attending for in-laboratory PSG. Of the 29 patients fulfilling all trial entry criteria, 2 withdrew consent for personal reasons and 1 died prior to randomisation (ruptured abdominal aortic aneurysm). Twenty-six patients were randomised and, of these, two withdrew immediately following the baseline assessment for personal reasons, and one withdrew after completion of the first limb of the study because of mask claustrophobia. One patient was excluded from the final analysis because multiple changes to drug therapy, instituted by the patient's attending physician, were deemed likely to influence trial endpoints. No time-order effects were observed.

### 5.4.1 Patient characteristics and continuous positive airway pressure use

Study patients were predominantly late middle-aged men (Table 5.1) maintained on optimal drug therapy for LV systolic dysfunction. The study population demonstrated moderately severe obstructive sleep apnoea, although only 8 patients (31%) complained of excessive daytime sleepiness (Table 5.2). Mean nightly CPAP and sham CPAP use were similar:  $3.5 \pm 2.5$  and  $3.3 \pm 2.2$  hours per night respectively ( $p=0.31$ ). Mean CPAP pressure applied was  $7 \pm 2$  cm H<sub>2</sub>O.

#### **5.4.2 Outcome data**

There were subjective but no objective improvements in daytime sleepiness with auto-titrating CPAP therapy (Table 5.3). No differences were demonstrated in other quality of life measures such as the SF-36 and Minnesota Living with Heart Failure questionnaire scores (Table 5.3, Figure 5.2). Similarly, there were no differences in cardiac function, exercise capacity or neurohormonal activation between CPAP and sham placebo (Table 5.3, Figure 5.3).

**Table 5.1**

Patient characteristics (n=26)

Age (years)	61±8
Sex (male:female)	23:3
Body mass index (kg/m <sup>2</sup> )	31±4
Hypertension	11 (42%)
Diabetes mellitus	7 (27%)
Hyperlipidaemia	16 (62%)
Smoking history	18 (69%)
Aetiology of CHF	
Ischaemic heart disease	12
Dilated cardiomyopathy	12
Other	2
Atrial fibrillation	8 (31%)
Drug treatment	
ACE / ARB	25 (96%)
Beta blockers	21 (81%)
Digoxin	11 (42%)
Diuretics	20 (77%)
Spironolactone	9 (35%)
NYHA class – II / III / IV	20 / 5 / 1

Mean±SD or number (%).

ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; NYHA, New York Heart Association.



**Table 5.2**

## Sleep assessment

Epworth Sleepiness Score	10±5
OSLER time (mins)	29±15
Obstructive apnoeas (per hour)	11±15
Central apnoeas <sup>#</sup> (per hour)	1(4)
Mixed apnoeas <sup>#</sup> (per hour)	0(1)
Hypopnoeas (per hour)	22±17
Apnoea/hypopnoea index (AHI)	36±23
Total sleep time (hours)	4.6±1.5
Sleep efficiency (%)	61±17
Oxygen saturation (%)	93±2
Oxygen desaturations ≥4% (per hour)	22±26

Mean±SD except #median (interquartile range); OSLER, Oxford SLEep Resistance test.

**Table 5.3**

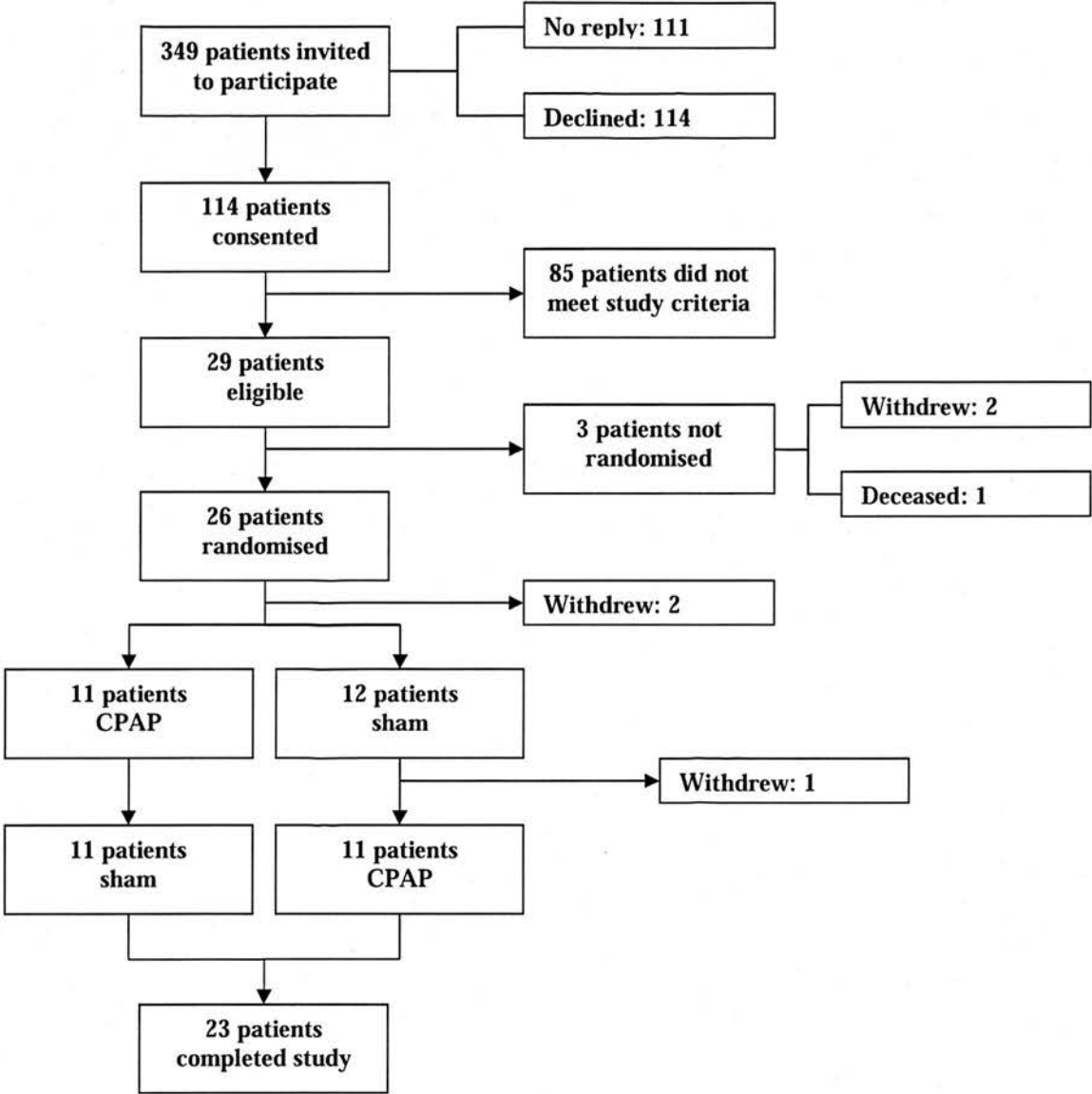
Effect of CPAP and sham CPAP on quality of life and cardiac function

	Baseline	Sham	CPAP	Treatment effect	P value
<b>Echocardiography</b>					
LVEDS (mm)	50±11	51±13	51±14	-0.1 (-0.4-0.3)	0.79
LVEDD (mm)	61±10	63±12	63±12	0.0 (-0.4-0.3)	0.83
FS (%)	18±7	20±8	19±6	0.1 (-3.3-3.6)	0.95
LVEF (%)	29±10	30±10	30±10	0.7 (-1.8-3.2)	0.56
<b>Exercise capacity</b>					
6 MW (m)	550±121	552±121	546±124	0 (-14-14)	0.98
Exercise time (mins)	10.0±2.3	9.7±3.0	9.8±3.1	0.2 (-0.3-0.7)	0.44
Peak VO <sub>2</sub> (mL/kg/min)	14.8±4.2	14.7±4.6	14.5±4.2	-0.2 (-0.9-0.4)	0.48
VE/VCO <sub>2</sub> slope	32±5	33±7	33±8	-0.3 (-1.9-1.4)	0.73
<b>Quality of life</b>					
Minnesota	38±27	34±28	36±29	1.0 (-4.3-6.4)	0.70
SF-36 – physical	34±16	35±14	34±14	-1.0 (-3.6-1.6)	0.43
SF-36 – mental	51±10	50±11	49±12	-0.5 (-4.2-3.2)	0.79
<b>Daytime sleepiness</b>					
ESS	10±5	8±5	7±4	-1 (-1.9-0.0)	0.04
OSLER (mins)	27±15	29±13	30±14	0.7 (-2.2-3.6)	0.63

Mean±SD except treatment effect (95% confidence interval). ESS, Epworth Sleepiness Scale; FS, fractional shortening; LVEDD, left ventricular end-diastolic dimension; LVEDS, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; OSLER, Oxford SLEep Resistance test; 6 MW, 6 minute walk test.

**Figure 5.1**

CONSORT diagram of trial recruitment.



**Figure 5.2**

Effect of CPAP and sham CPAP on quality of life measures (SF-36).

PF, physical function; R-P, role – physical; R-E, role – emotional; SF, social function; BP, bodily pain; MH, mental health; V, vitality; GH, general health.

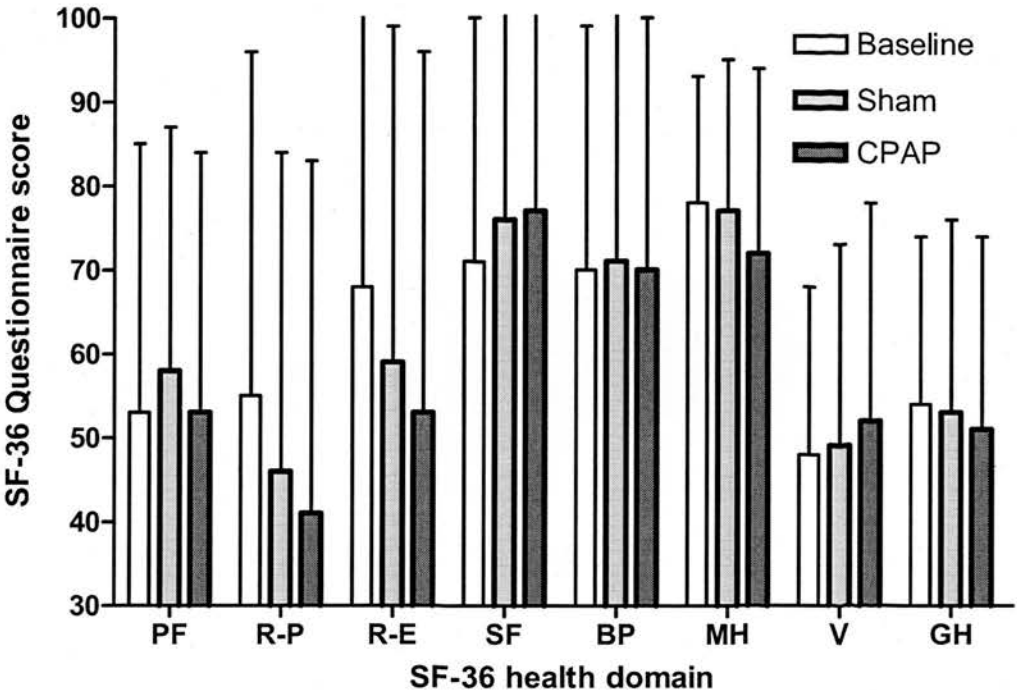
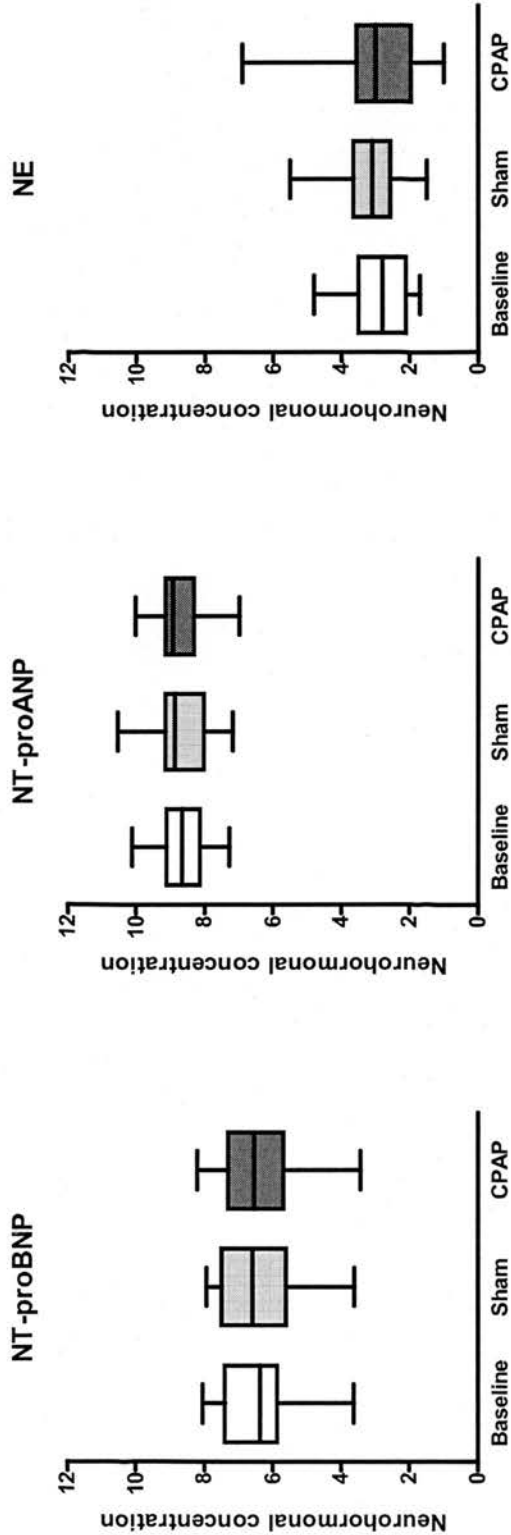


Figure 5.3

Effect of CPAP and sham CPAP on plasma neurohumoral measures of cardiac function.



NT-proBNP, N-terminal pro-brain natriuretic peptide; NT-proANP, N-terminal pro-atrial natriuretic peptide; NE, norepinephrine. NT-proBNP and NT-proANP are logarithmically transformed and data are presented as mean, interquartile ranges and 95% confidence intervals.

## 5.5 DISCUSSION

We have conducted the first randomised double blind placebo controlled cross-over trial of auto-titrating nocturnal CPAP therapy in patients with CHF and OSA. In contrast to smaller previous trials, CPAP improves daytime sleepiness but not other subjective or objective measures of CHF severity. These data suggest that the potential therapeutic benefits of CPAP in CHF are achieved by alleviation of OSA rather than by improvement in cardiac function. However, the efficacy of CPAP as a treatment for patients with CHF and OSA may be limited in part by poor patient tolerability and compliance.

Important advances have been made in the management of patients with CHF in the last two decades. A range of therapeutic options that are known to impact on symptoms, quality of life and prognosis are now available to the physician. However, the prevalence of CHF continues to rise, associated morbidity and mortality rates remain high, and the financial burden to healthcare systems is great.(3) The identification of potential exacerbating factors and possible therapeutic targets therefore remains extremely important. OSA is one such factor that commonly co-exists with CHF, may contribute to disease progression and can be potentially targeted by CPAP therapy.

Two recently published randomised controlled trials in patients with CHF and OSA are encouraging.(93;142) These trials reported that CPAP therapy improved LVEF, systolic blood pressure and symptoms. However, these studies had important

limitations including the single-blind design and the small numbers of patients (n=12-19 *per* intervention group) completing study protocols. Some of the study findings were not entirely consistent given that there were no changes in peak VO<sub>2</sub> or NYHA class despite improvements in LVEF.

Previous trials of CPAP have used non-intervention control groups raising concerns regarding potential placebo effects and adequate blinding. This is a particular problem when using device interventions that require training, supervision and close liaison with healthcare professionals. Prior work with CPAP in patients with OSAHS has revealed a powerful placebo effect, reducing ESS score by 2 points and improving other quality of life measures.(127;140) Failure to control for a placebo effect could therefore overestimate differences in endpoints between intervention and non-intervention groups. We therefore used sham CPAP as a placebo control and, in our study, there were no differences in compliance or drop-out rates between sham and active CPAP limbs suggesting that patient blinding was maintained and that an effective placebo was indeed employed.

Results of parallel group studies involving small numbers of patients are susceptible to bias introduced by baseline differences between control and treatment groups as well as by outliers. For example, the control group in the Kaneko *et al* trial had significantly worse OSA than the treatment group at baseline and this may have led to worsening of cardiovascular variables over the conduct of the trial.(142) Decisions whether to include or exclude outliers in statistical analysis, or inadequate matching of outcome variables at study entry, such as LVEF and AHI thresholds,

may markedly alter statistical results and reported outcomes. Indeed, the impact of outliers and the methods of statistical analysis on the results of the study by Mansfield *et al* have been discussed elsewhere.(217)

Determining the effects of CPAP on cardiovascular outcomes in patients with CHF and OSA remains an extremely important clinical question. The present study utilized a robust randomised double-blind placebo controlled crossover trial design that enables patients to act as their own control, thus reducing between-subject variability, avoiding the need for matched control subjects, and increasing statistical power. Indeed, our analysis of 23 patients yields a power 2-4 times greater than that of the previously published parallel group studies.(20;21) The entry criteria and endpoints for the current study were well-defined and clinically relevant. Robust symptomatic and quality of life assessments are vital when considering CPAP as a potential treatment as the patient's perception of benefit is a major determinant of future compliance with therapy. Peak  $\text{VO}_2$ ,  $\text{VE}/\text{VCO}_2$  slope and NT-proBNP all provide important prognostic information in CHF.(184-186) LVEF also provides useful information but correlates poorly with symptoms and functional limitation in CHF.(187) Major treatment advances in the management of CHF patients, such as the introduction of ACE inhibitors, beta-blockers and, more recently, biventricular pacing have been shown to improve these parameters and subsequently, in large randomised controlled trials, to reduce hospitalisation rates and mortality.(9;13;15;16)



We have shown small and clinically modest improvements in subjective, but not objective, measures of daytime sleepiness with CPAP that are not due to a placebo effect. This is perhaps not surprising as the aetiology of sleepiness in patients with CHF is clearly multifactorial. In contrast to previous work, no improvements in quality of life measures, functional capacity or other markers of CHF severity were identified with CPAP therapy in this patient group. This is despite the greater severity of both CHF and OSA in our study population compared to that of Mansfield *et al.*(144)

Compliance with CPAP therapy in this study was reasonable, particularly when the reduced total sleep time is considered, but was poorer than that achieved in other studies.(142;144) This was despite careful education, initiation of treatment in-laboratory and the provision of ongoing support, suggesting that CPAP may not be acceptable to a proportion of patients with CHF and OSA. Previous work in patients with OSAHS has shown that there is a need to derive symptomatic benefit from CPAP in order to accept the associated discomfort and inconvenience. Accordingly, compliance and long-term usage in patients with mild OSAHS is poor.(140) Similarly, patients with CHF and OSA who do not have excessive daytime sleepiness, or whose sleepiness is due to factors other than OSA, may not comply with CPAP therapy. We did not find the ESS and OSLER tests to be helpful in identifying which patients with CHF and OSA would derive symptomatic benefit from CPAP.

### 5.5.1 Study Limitations

The study protocol did not include follow-up PSG. Our aim was to investigate whether auto-titrating CPAP was a tolerable and effective treatment for patients with CHF and OSA rather than whether auto-titrating CPAP reduced AHI. Whilst not routinely performed in the clinical setting, we accept that a follow-up PSG would have been helpful to ensure efficacy of the treatment intervention.

Inadequate reduction in AHI, due to limited subject compliance, would be a possible explanation for the lack of efficacy of CPAP therapy for cardiovascular endpoints. However, it is important to note the low total sleep times observed in this study: in itself an interesting and important finding in patients with CHF. Moreover, CPAP use was greater than that observed in our previous studies of patients with OSAHS where we have shown that CPAP therapy produced significant improvements in both quality of life and cardiovascular endpoints.(76;140) Furthermore, Bradley *et al* demonstrated sustained improvements in LVEF and plasma norepinephrine concentrations with comparable nightly CPAP use (3.6 hours at 12 months), albeit in CHF patients with central sleep apnoea rather than OSA.(109) We also accept that the duration of treatment in the present study may have been insufficient to demonstrate effects on cardiovascular endpoints although previous work has shown benefits after only 4 weeks of treatment.(76;125;142;143)

We used the American Academy of Sleep Medicine definition of significant respiratory events which does not require oxygen desaturation when flow is measured by nasal pressure rather than thermal signal.(30) Our system recorded flow

by nasal pressure in addition to thoraco-abdominal movement and these signals were used to identify hypopnoeas. Hypopnoeas cannot be differentiated with certainty between central or obstructive from surface techniques and therefore we report events per hour rather than central and obstructive events separately. The study cohort showed a moderate degree of OSA with the majority of respiratory events being hypopnoeas, a proportion of which may have been central in nature. Based on these results, it is not possible to exclude benefit from auto-titrating CPAP in patients with concomitant severe OSA and CHF.

### **5.5.2 Conclusions**

Auto-titrating nocturnal CPAP improves subjective daytime sleepiness but not other quality of life measures or markers of CHF severity in patients with CHF and OSA. These data suggest that symptomatic benefit in this patient group is achieved by alleviation of OSA rather than by improvement in cardiac function. The efficacy of CPAP as a treatment for patients with CHF and OSA may in part be limited by poor patient tolerability and compliance. On the basis of our findings, we believe that this approach is unlikely to provide a major therapeutic impact on the morbidity and mortality associated with chronic heart failure.

## **CHAPTER 6**

### **CONCLUSIONS AND FUTURE DIRECTIONS**

## **6.1 DETECTION AND DIAGNOSIS OF SLEEP-DISORDERED BREATHING IN PATIENTS WITH CHRONIC HEART FAILURE**

There is currently no accepted, widely available screening tool for SDB in patients with CHF. PSG is relatively expensive, not widely available and demand currently exceeds supply, at a time when only a minority of patients with CHF is investigated and treated for SDB.(113)

Portable limited sleep study systems are both useful and cost-effective in the diagnosis of OSAHS.(114-117;119;218) For the first time, a limited sleep study system has been evaluated, performing both synchronous in-laboratory (PSG versus limited) and home studies, in the diagnosis of SDB specifically in patients with CHF.(24) The limited sleep study compared well with PSG when tested under identical patient and environmental conditions but much less so when tested in the home setting. This finding can be explained by a number of technical and situational factors which are further exacerbated in patients with CHF. The limited sleep study system does not record sleep and, as such, tends to underestimate the PSG AHI.(22;115;116) Patients with CHF have lower total sleep times and sleep efficiency and, as a result, there is even greater underestimation of respiratory event rate.(22-24) The symptoms of CHF, in addition to more advanced age and associated co-morbidity, side-effects of medication and psychosocial effects of chronic illness all contribute to poor sleep. These symptoms also fluctuate further contributing to night-to-night variation in respiratory events.(198) Furthermore, patients may sleep better in the home environment compared to the sleep laboratory and this may

influence body position and subsequently respiratory event rate.(199) Therefore, it is possible that studies conducted in the home environment, rather than in-laboratory, are a more accurate reflection of the true burden of SDB. These factors should be taken into consideration when considering potential screening or diagnostic tools for SDB in patients with CHF.

Health care professionals need to be alert to the presence and clinical relevance of SDB in patients with CHF. There is a need for greater awareness and education for both patients and clinicians with respect to both good sleep hygiene and SDB. Based on current available data, PSG should be considered in those patients with CHF who complain of excessive daytime sleepiness despite optimal modern CHF therapy. There is insufficient evidence of treatment benefit presently to support widespread screening for SDB in patients with CHF. Additional work is required in the development of screening tools for the identification of SDB in large populations. Alternative screening tools such as nocturnal pulse oximetry and heart rate variability are currently subjects of research but have important limitations.(201;219-223) It appears that the need to determine sleep is of greater importance in patients with CHF and the development of a limited sleep study system with a modified EEG may prove helpful in this regard.

## **6.2 CONTEMPORARY PREVALENCE OF SLEEP-DISORDERED BREATHING IN PATIENTS WITH CHRONIC HEART FAILURE**

SDB remains relatively common, but with lower prevalence than previously reported, in patients with symptomatic stable CHF due to left ventricular systolic dysfunction on optimal contemporary medical therapy.(23;49;52;55-60) However, contrary to previous data, SDB is predominantly obstructive in aetiology, and CSA and CSR are now rare in this setting. It is likely that this lower prevalence of SDB, and the observed reduction in CSA, is due to improvements in the modern treatment of patients with CHF.

Recent data, however, are conflicting with an estimated overall prevalence of SDB of between 24 and 71% with no consensus on the predominant type of SDB.(55-60) This discrepancy in findings in similar patient cohorts maintained on comparable medical therapy may be explained by lack of standardisation with respect to type of sleep study, scoring criteria and diagnostic thresholds.

Classification of respiratory events may be challenging, particularly as obstructive, central and mixed events may all exist in the same patient.(94;95) There is a lack of consensus regarding the definition and classification of hypopnoeas in particular and this may influence the designated predominant type of SDB. The distinction between OSA and CSA is clinically important because it influences treatment strategy.

There is considerable overlap in the symptoms of CHF and SDB, and, whilst patients with CHF have objectively measured daytime sleepiness, few complain of it.(22;49;195) Indeed, in this study cohort, the presence of SDB did not impact on symptoms, functional status or measures of severity of CHF. The ESS and BMI were not helpful in predicting the presence of SDB. It is difficult therefore to identify SDB clinically in patients with CHF and clinicians should be alert to the requirement for sleep studies to diagnose SDB in this patient population.

As therapies for CHF continue to advance, there will be a need to reassess at intervals the prevalence, pathophysiology and clinical relevance of SDB to guide research and clinical activity. OSA, rather than CSA and CSR, is currently the predominant type of SDB in patients with CHF, and with risk factors for OSA and CHF in the general population increasing, the prevalence is likely to continue to rise. OSA should therefore now be the focus of attention. Furthermore, there is an urgent need for greater agreement and standardisation in scoring and classification criteria for SDB in CHF to enable meaningful comparisons and appropriate treatment decisions to be made. Without this, it will be difficult to further advance knowledge in this important area and enable the transition from research into clinical practice.



### **6.3 TREATMENT OF OBSTRUCTIVE SLEEP APNOEA IN PATIENTS WITH CHRONIC HEART FAILURE**

In the first randomised placebo-controlled crossover trial of auto-titrating nocturnal CPAP in patients with CHF and OSA, CPAP improves subjective daytime sleepiness but not other quality-of-life measures or markers of CHF severity.(210) These data contrast with smaller previous trials and suggest that the potential therapeutic benefits of CPAP in CHF are achieved by alleviation of OSA rather than by improvement in cardiac function.(142;144) Compliance with CPAP therapy was reasonable, considering the reduced total sleep time, but poorer than that achieved in some other studies.(142;144) This was despite careful education, initiation of treatment in-laboratory and provision of ongoing support, suggesting that CPAP may not be acceptable to a proportion of patients with CHF and OSA. Patients need to perceive symptomatic benefit from CPAP in order to accept the associated discomfort and inconvenience, which persists despite advances in device technology. Studies of CPAP in patients with OSA, but no excessive daytime sleepiness, have failed to show improvements in symptoms or neuro-cognitive function.(224) Accordingly, patients with OSA and CHF who do not have excessive daytime sleepiness, or whose sleepiness is due to other factors, may not comply with therapy. Therefore the efficacy of CPAP as a treatment for OSA in patients with CHF may be limited in part by poor patient tolerability and compliance.

It can be seen that OSA is highly prevalent in patients with CHF,(55-60) and via a variety of haemodynamic, autonomic and vascular effects, may contribute to the

progression of CHF.(74;76-82;225-228) There are currently no data to suggest that drug therapies used to treat CHF impact on the severity of OSA.(229) General measures such as weight loss and avoidance of alcohol and sedatives may be beneficial however.(43;44;230)The available data regarding the potential benefits of treating OSA with CPAP in patients with CHF are limited and conflicting.(142-146;210) Studies have involved small numbers of patients conducted in single centres with treatment of 1-3 months duration. Based on these data, it is reasonable to recommend a trial of CPAP therapy for those patients with OSA and CHF with excessive daytime sleepiness to improve symptoms and quality of life but not to improve cardiac function, morbidity or mortality. Accordingly, for those patients with OSA and CHF but without excessive daytime sleepiness, CPAP is not likely to be either of significant symptomatic benefit or well-tolerated. The occasional finding of CSA on sleep studies should prompt intensive efforts to optimise and ensure compliance with CHF therapies. Presently there is no evidence to support the use of CPAP in these patients as CPAP has not been shown consistently to improve symptoms or, importantly, morbidity and mortality.(104;109;158)

Currently, there are no large-scale trials investigating the effects of medium or long-term treatment of OSA on cardiovascular function, morbidity or mortality in patients with CHF. This work highlights the need for multi-centre randomised controlled trials with adequate power to address these important questions. Such trials will pose difficulties in design and execution in view of the large numbers of participants required, the lack of access to specialist sleep centres and the relatively intensive nature of the intervention. Concerns have been raised regarding both the ability to

maintain and the ethics of administering true placebo or sham CPAP over a prolonged period;(231) however based on the current evidence the number of patients with CHF and conventional indications for treatment of OSA is small. In order to facilitate such research greater collaboration will be required between respiratory and sleep physicians and cardiologists, and also between clinicians and industry.

## **6.4 SYSTEMIC HYPERTENSION IN PATIENTS WITH OBSTRUCTIVE SLEEP APNOEA AND CHRONIC HEART FAILURE**

In patients with normal LV systolic function, the results of large epidemiological studies support a causative role for OSA in the development of systemic hypertension, independent of other potential confounding variables.(33;80;211-213) Furthermore, animal studies, where dogs have been exposed to experimental OSA for a period of several weeks, have shown that OSA leads to the development of systemic hypertension, left ventricular hypertrophy and left ventricular systolic dysfunction.(79;232;233) Hypertension itself is the commonest risk factor for the development of CHF in longitudinal epidemiological studies.(3;234) The failing left ventricle is particularly sensitive to small increases in afterload and, accordingly, control of blood pressure is extremely important in patients with CHF.

Treatment of OSA with CPAP has been shown to lower both daytime and nocturnal blood pressure in patients with normal LV systolic function.(76;124;125) Whilst these reductions in blood pressure have been modest in magnitude, small but maintained improvements in blood pressure are known to significantly reduce the incidence of cardiovascular and cerebrovascular disease.(235-238) It is possible therefore that treatment of OSA with CPAP improves blood pressure control which may then translate into improvements in overall cardiovascular prognosis.

The development or exacerbation of systemic hypertension associated with OSA presents one potential mechanism by which the progression of CHF may be accelerated. In patients with OSA and CHF due to impaired LV systolic function,

nocturnal blood pressure remains above waking values and elevated daytime blood pressure has been shown to correlate positively with increasing AHI.(74;239) Small studies of CPAP in patients with OSA and CHF have shown conflicting effects on systolic blood pressure.(142;144)

Currently, it is unknown whether treatment of OSA with CPAP in patients with CHF due to LV systolic impairment produces sustained reduction in systemic blood pressure and whether this in turn might confer any benefit on cardiovascular morbidity and mortality. Whilst such a study would require very large numbers of participants to ensure adequate statistical power, this is a potential area of future research interest.

## **6.5 NON-INVASIVE VENTILATION IN PATIENTS WITH CHRONIC HEART FAILURE: AN UPDATE**

At present, sleep apnoea is not a specific therapeutic target in patients with CHF, despite its high prevalence and impact on morbidity and mortality, and its management is not addressed in contemporary evidence-based guidelines.(1;7) This position is appropriate in view of concerns regarding potential early harm with CPAP, inadequate treatment of central apnoeas with current CPAP devices and a lack of randomised clinical trial data demonstrating improvement in cardiovascular outcomes with targeted therapy for SDB in patients with CHF. However, the possibility of clinical benefit and the lack of other treatments for SDB ensure this is a vital and active area of ongoing research. More than thirty clinical trials active in the area of SDB and CHF are registered in ClinicalTrials.gov, the ISRCTN registry and the WHO International Clinical Trials Registry Platform. These include further trials investigating the prevalence of SDB in CHF, the utility of various screening tools and the effects of CPAP on various measures of cardiovascular function. In addition, trials of ASV, bi-level non-invasive ventilation, cardiac resynchronisation therapy, overdrive pacing, nocturnal O<sub>2</sub>, developmental drugs and exercise in patients with CHF and SDB are also registered. Other groups are investigating the effects of CPAP on cardiac remodeling and metabolism, vascular function and coagulation. However, none is designed to answer the crucial question of whether specific treatment of SDB in patients with CHF does indeed reduce cardiovascular event rates.

## **6.6 CONCLUSION**

SDB is common and clinically relevant in patients with chronic heart failure. The relationship between SDB and cardiovascular disease is extremely complex and not yet clearly defined. Better understanding of this relationship, gained from mechanistic studies, epidemiological research and clinical trials, has the potential to benefit a large proportion of the population. Closer collaboration is required between sleep physicians and cardiologists, and between clinicians and industry, both to raise awareness of the clinical relevance of SDB and to facilitate greater well-designed and coordinated research activity.

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## APPENDIX

### DISSEMINATION OF RESEARCH FINDINGS

#### PUBLICATIONS

**Smith LA**, Gardner RS, Vennelle M, McDonagh TA, Denvir MA, Douglas NJ, Newby DE. Auto-titrating continuous positive airway pressure in patients with obstructive sleep apnoea and chronic heart failure: a randomised placebo controlled trial. *Eur Heart J* 2007;28:1221-7.

<http://eurheartj.oxfordjournals.org/cgi/content/abstract/28/10/1221>

**Smith LA**, Chong WS, Vennelle M, Denvir MA, Newby DE, Douglas NJ. Diagnosis of sleep apnoea in patients with chronic heart failure: evaluation of a portable limited sleep study system. *J Sleep Res* 2007;16:428-435.

<http://www.blackwell-synergy.com/doi/abs/10.1111/j.1365-2869.2007.00612.x>

**Smith LA**, Vennelle M, Denvir MA, Douglas NJ, Newby DE. Sleep-disordered breathing in patients with chronic heart failure: contemporary prevalence and characteristics. Submitted.

## **PRESENTATIONS**

American Thoracic Society Annual Scientific Congress 2005, San Diego, California,  
U.S.A.

European Society of Cardiology Annual Scientific Congress 2005, Stockholm,  
Sweden

Scottish Cardiac Society 2005, Turnberry, Scotland

British Cardiac Society 2006, Glasgow, Scotland

European Society of Cardiology Annual Scientific Congress 2007, Vienna, Austria